JOURNAL OF THE

American Geriatrics Society

Official Journal of the American Geriatrics Society

Volume IX *November, 1961* **Number 11**

CARDIAC ARREST AND CARDIAC RESUSCITATION IN THE AGED

HARRY B. GREENBERG, M.D.*

The Department of Medicine, Touro Infirmary, New Orleans, Louisiana

The incidence of cardiac arrest is increasing yearly as improved techniques of surgery and anesthesia permit operations on aged and poor-risk patients, and directly on the heart and great vessels. Estimates place the number of such cases of cardiac arrest at 3,000 to 10,000 yearly, or from 1 to 5 cases for every 5,000 operations (1–3). Although resuscitative measures are often dramatically successful, thoracotomy and direct cardiac massage may be followed by cardiac injury, bilateral pulmonary atelectasis, pleural effusion, empyema and bronchopneumonia. Patients surviving cardiac arrest without critical cerebral injury may succumb to cardiac and pulmonary complications incident to the resuscitative procedures.

This article is a review of 13 cases of cardiac arrest in older patients.

PATIENTS AND METHODS

The 13 patients (ages, 59–86) included all those in this age group with diagnoses of cardiac standstill or ventricular fibrillation after surgery or anesthesia, who were hospitalized at the Touro Infirmary from 1953 through 1960 (Table 1). They comprised one-fifth of all the patients with cardiac arrest who were hospitalized during this even-year period.

One patient was anesthetized with intravenous sodium thiopental, the others received inhalational anesthesia. The anesthetic was administered through an endotracheal tube to 11 patients. All but 1 patient (No. 11) received muscle relaxants during anesthesia—10, succinylcholine and 2, curare. Although over-anesthetization was an important factor, no single anesthetic, mode of administration or pre-anesthetic medication was predominantly associated with cardiac arrest.

Three patients underwent emergency operations for hemorrhage in the upper gastrointestinal tract. Two others received over 2 liters of bank blood during surgery. However, no deaths were caused by uncontrolled hemorrhage. Though 11 patients had arteriosclerotic or hypertensive heart disease, none was in a state of heart failure at the time of operation. Two patients were obese, and one of them also had diabetes mellitus.

CLINICAL FINDINGS

Cardiac standstill occurred in 12 patients and ventricular fibrillation in 1 (Patient No. 4).

In 9 of the 13 patients the common premonitory sign of cardiac arrest was an

* Instructor in Medicine, Tulane University School of Medicine, New Orleans.
Address: 1435 Delachaise Street, New Orleans 15, La.

TABLE 1

Data on 13 Cases of Cardiac Arrest

Patient		Diagnosis/Procedure	Premonitory Fall in B.P.	Amt. of Blood Transfused* (ml.)	Survival Time
Case No.	Age (yrs.)				
1	70	Obstruction of small intestine	+	1,000	11 days
2	71	Gastro-intest. hemorrhage	+	2,000	2 days
3	64	Incarcerated femoral hernia	+		12 days
4	78	Obstruction of small intestine			7 hrs. and 40 mins.
5	60	Retroperitoneal lyomyosarcoma	+	4,000	22 mins.
6	69	Peritonitis; disruption of rectosigmoid anastomosis	+	500	1 day
7	59	Exploratory laparotomy			Recovered
8	61	Gastro-intest. hemorrhage	+	500	2 hrs.
9	70	Gastro-intest. hemorrhage	+	500	Recovered
10	70	Bronchogenic carcinoma	+	2,250	28 hrs.
11	60	Chronic tonsillitis			Recovered
12	85	Hip fracture, open reduction	+	1,000	0
13	86	Peritonitis; diverticulitis			0

* Before cardiac arrest.

abrupt, transitory fall in blood pressure; the blood pressure quickly rose again after administration of vasoconstrictor drugs and blood transfusions. This premonitory change occurred from two hours to a few minutes before the cardiac arrest took place. Patient No. 3 went into a state of shock during the induction of anesthesia; she recovered after a temporary interruption of the anesthetic and the inhalation of oxygen; forty-five minutes later cardiac arrest occurred during the manipulation of an incarcerated hernia. Patient No. 10 experienced two abrupt falls in blood pressure during operation; each responded to vasopressor drugs and blood transfusions; thirty minutes later cardiac arrest occurred at a time when traction was being applied to a bronchus. In 2 patients the blood pressure was unstable early in the course of surgery, rising and falling precipitously, but it had been stabilized before cardiac arrest took place; in one patient the cardiac arrest was preceded by sinus bradycardia, and in the other (Patient No. 4) by ventricular tachycardia.

Two patients suffered cardiac arrest following a rapid increase in the flow of anesthetic. Patient No. 7 became rigid just before the peritoneum could be incised, so ether was forced to hasten relaxation; cardiac standstill followed. Immediate artificial respiration and inhalation of oxygen restored effective heart action before a thoracotomy could be performed. The operation was not continued, and the patient recovered completely. Patient No. 9, during closure of the peritoneum, began to strain; the flow of anesthetic was rapidly increased; cardiac arrest occurred shortly afterward, necessitating thoracotomy and direct cardiac massage.

In 2 anesthetized patients, cardiac arrest occurred before surgery began—

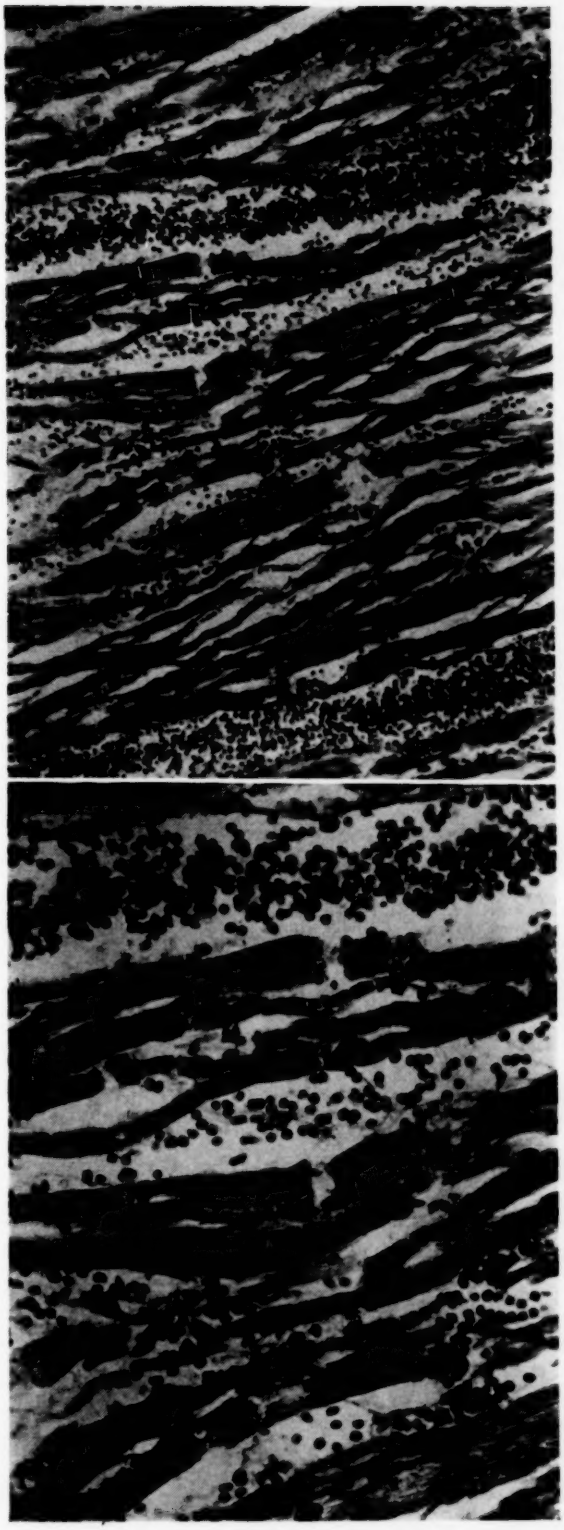

FIG. 1. *Above:* Section through myocardium showing interstitial hemorrhages with fragmentation and disruption of fibers. (H & E stain, reduced from ×140.) *Below:* Same section, higher magnification. (H & E stain, reduced from ×440.)

during induction of anesthesia, and shortly after anesthetization, respectively. Seven patients suffered cardiac arrest either during completion of the operation or in the immediate postoperative period. In Patient No. 5, cardiac standstill occurred while he was in the recovery room; he had regained consciousness just before onset. In Patient No. 4, ventricular fibrillation developed in association with transfer from the operating table to a litter. The other 5 patients suffered cardiac arrest in the latter part of the operation, during closure of the skin or peritoneum.

FIG. 2. Section through cerebral cortex (Case 3) showing degeneration of neurones of first cortical cell layer; other neurones have pyknotic nuclei. (H & E stain, ×140.)

The 3 patients surviving cardiac arrest recovered without permanent injury to the central nervous system. Nine patients received direct cardiac massage; 8 through a thoracotomy incision and 1 through a ruptured diaphragm. The stomach of the latter patient subsequently herniated through the ruptured diaphragm into the thorax; at necropsy it was found to have compressed the left lung to one-third of the normal volume.

NECROPSY FINDINGS

Nine necropsies were performed. In one heart, there was conspicuous evidence of trauma from direct cardiac massage. Large ecchymoses and extensive epicardial hemorrhages were noted over both ventricles, particularly over the apex of the right ventricle. Linear hemorrhages were scattered throughout the myocardium in association with necrosis, disruption and fragmentation of fibers (Fig. 1). Foci of hemorrhage also were found within the interventricular septum.

Two of the hearts showed healed infarcts with fibrous replacement; one area of fibrosis was surrounded by a hemorrhage. Myocardial hypertrophy, fibrosis and varying degrees of coronary sclerosis were also common.

Examination of the central nervous system in Patient No. 3, who survived twelve days after a cardiac arrest without regaining consciousness, showed congestion of the small meningeal vessels and subcortical capillaries. Some cortical neurones had degenerated completely (Fig. 2), and the cortical cell layers were distorted. Glial proliferation, pigment-containing macrophages, a perivascular hemorrhage, and neutrophilic exudates were additional evidence of injury caused by anoxia. Perivascular cuffing and neurone degeneration were noted in the basal nuclei.

Pulmonary pathologic lesions were a prominent finding in all the necropsies on patients who died after direct cardiac massages. Severe, bilateral, lobar

TABLE 2

Pulmonary Pathologic Findings in 5 of 9 Necropsies

Patent No.	Pulmonary Atelectasis		Pleural Fluid (ml.)	
	Left lung	Right lung	Left side	Right side
1	Upper lobe (½) Lower lobe	Lower lobe	1500	250
2	Lower lobe (½)	Lower lobe Middle lobe	100	100
3	Lower lobe Upper lobe (½)	Lower lobe (½)	500	400
4	Lower lobe	Lower lobe	700	300
5	Lower lobe Upper lobe (½)	Lower lobe (½)	100	—

atelectasis was observed in 5 cases (Table 2), with extensive bilateral bronchopneumonia in 2 cases. In one of the latter patients the bronchopneumonia was accompanied by a purulent pleural exudate. Large serosanguinous pleural effusions were found in 3 cases.

COMMENT

The outstanding premonitory sign of cardiac arrest in this series was a sudden fall in blood pressure that occurred early in the operation. The other premonitory signs were sinus bradycardia and ventricular tachycardia.

Occasionally, withdrawal of anesthesia upon the appearance of these premonitory signs may avert cardiac arrest. The return of vagal activity (bradycardia) during lengthy operations indicates the need for additional atropine, particularly when an endotracheal tube has been removed (2, 4).

Obesity predisposes to cardiac arrest, since more anesthetic is needed to anesthetize the obese patient and therefore the postanesthetic recovery period is longer. Inhalational anesthetics and muscle relaxants depress the heart, and concentrations of anesthetic safe to the normal heart are dangerous to the diseased or oxygen-deprived myocardium (5).

Lack of oxygen and excess of carbon dioxide are the common causes of cardiac arrest. They enhance reflex vagal activity and depress both the myocardium and conduction system of the heart (6). Obstruction of the airway, blood loss, impaired venous return and the position of the patient on the operating table may cause hypoxia during anesthesia (7). Electrolyte imbalance, direct stimulation of the heart and drug sensitivity are additional contributory causes of cardiac arrest (3, 8, 9).

During anesthesia, shallow ineffective respiration and poor alveolar ventilation may result in hypoxia, accumulation of carbon dioxide and respiratory acidosis. A rise in extracellular potassium concentration often accompanies hypercapnea. This rise reaches its peak in the immediate posthypercapneic period, at the end of anesthesia when the patient breathes room air. The extracellular potassium concentration soon returns to a normal level as the excess potassium is translocated into body tissue (10, 11).

Nine of the patients with cardiac arrest received transfusions during surgery; 5 received 1 liter or more of citrated bank blood. After long storage, the concentration of extracellular potassium in bank blood is high. When large quantities of bank blood are transfused during surgery, this potassium plus that released from endogenous sources may raise the extracellular potassium concentration to dangerous levels (12). The citrate in transfused blood may also potentiate the toxic effect of potassium on the heart by causing a temporary alteration in the calcium-potassium ratio outside the myocardial cell (10).

The heart that stops suddenly may respond to a sharp blow on the anterior chest wall. No further delay is warranted; immediate artificial respiration and cardiac massage are necessary. The four-minute interval between circulatory arrest and permanent injury to the central nervous system may be shortened in older patients by pre-existing cerebral hypoxia (13–15). Vigilance is essential,

particularly during the latter part of the operation and the immediate postoperative period.

Kouwenhoven *et al.* (16) have reported successful resuscitation with the use of a closed-chest method of cardiac massage and external electrical cardiac defibrillation (17). The pulmonary complications in many patients in our series probably resulted from thoracotomy, mediastinal trauma from direct cardiac massage, hypoxia and heart failure. With the aid of frequent chest roentgenograms the physician can detect lobar atelectasis, pleural effusion, bronchopneumonia and empyema. The use of such remedial measures as tracheostomy, bronchoscopic aspiration, thoracentesis and additional antibiotic therapy may reduce the fatality rate. Careful cardiac massage with an intact pericardium may lessen cardiac injury.

SUMMARY

The incidence of cardiac arrest during surgery is increasing. In the group of 13 older patients reported here, a frequent premonitory sign of cardiac arrest was an abrupt fall in blood pressure that occurred earlier in the course of operation. Blood loss necessitating large replacement transfusions predisposes to cardiac arrest.

Nine necropsies were performed. In these 9 patients, there was histopathologic evidence that cardiac resuscitation with thoracotomy and direct cardiac massage was followed by severe bilateral lobar atelectasis, pleural effusion and bronchopneumonia. Recognition and treatment of the pulmonary complications may reduce the high fatality rate in these cases.

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THE AGING INTESTINAL TRACT: ESOPHAGUS, STOMACH AND SMALL BOWEL*

C. WILMER WIRTS, M.D.†

Jefferson Medical College, Philadelphia 7, Pennsylvania

The symptoms that most often cause patients to seek aid in the general physician's office or in the diagnostic clinic are those referable to the gastro-intestinal tract (1). However, many of these symptoms are due to functional disturbances which rarely cause death and have their highest incidence in the younger age group. After the fifth decade the incidence of organic disease rises.

The most common cause of death from disease of the digestive system is cancer. Statistically it has been shown that approximately half of all deaths due to cancer are attributable to neoplastic involvement of the digestive organs and peritoneum. Other disorders often leading to death are hepatic disease, ulcer, intestinal obstruction, diverticulitis of the colon, and pernicious anemia.

This report concerns our own observations on the incidence of gastro-intestinal disturbances in the older patient.

GASTRO-INTESTINAL DISORDERS

A survey was made of the records of 348 patients examined for gastro-intestinal complaints during the year 1960. The diagnoses and ages are listed in Table 1. The most frequent cause of symptoms in this series was a functional bowel disorder. Next in frequency were peptic ulcer, hiatal hernia and diverticulitis of the colon. There was a definite increase in the incidence of hiatal hernia, gastritis, cirrhosis and diverticulitis in the patients who were past 50 years of age. In each of these groups, more than 60 per cent of the patients were past the fifth decade.

The records of patients admitted to the Jefferson Medical College Hospital for the years 1958 through 1960 were also reviewed, and in 1,742 cases the incidence of hiatal hernia, diverticulitis of the colon, cirrhosis, gastritis, cancer of the stomach, esophagitis, pernicious anemia and achlorhydria were recorded in relation to the patient's age. The results, listed in Table 2, show the greater frequency of all of these illnesses in patients over 50. Diverticulitis of the colon, pernicious anemia and achlorhydria occurred almost exclusively in older patients.

From these data there appears little doubt that there is an increased incidence of gastro-intestinal disease with advancing age; however, neither these data nor the reports of others indicate a wearing-out process in the intestinal tract. In fact, when consideration is restricted to the esophagus, stomach and small intestine, there is no evidence of an aging process, with the possible exception of a decreased gastric secretory capacity.

* Presented before the American College of Physicians, Postgraduate Course No 11—"Problems of Growth and Aging"—April 11-14, 1961, at the Lankenau Hospital, Philadelphia, Pa.

† Associate Professor of Medicine, Jefferson Medical College.

TABLE 1

Incidence of Disease According to Age Groups in 348 Patients (Year 1960)

No. of Cases	Diagnosis	Age Group							
		10–20	21–30	31–40	41–50	51–60	61–70	71–80	Over 80
84	Functional bowel disturbance	2	3	10	24	24	16	5	
48	Ulcer		2	7	19	13	5	2	
45	Hiatal hernia			5	10	18	11	1	
29	Diverticulitis coli			1	1	14	11	1	1
29	Nongastro-intest. disease			1	4	9	8	5	2
20	Gastritis			1	6	10	2	1	
17	Ulcerative colitis		4	3	5	2	2	1	
16	Cancer				6		7	2	1
14	Biliary-tract disease			2	7	3	2		
13	Cirrhosis				1	4	7	1	
10	Esophagitis		1		3	3	3		
9	Pancreatitis		1	1	3	2	2		
9	Malabsorption syndrome			2	4		2	1	
5	Diabetes					1	4		

348 Total

TABLE 2

Incidence of Disease in Patients over 50 Years of Age

(1,742 patients; years 1958–1960 inclusive)

Diagnosis	Number of Patients (all ages)	Number of Patients	
		Over 50 years of age	Per cent
Hiatal hernia	677	455	67.2
Diverticulitis coli	364	324	90.0
Cirrhosis of liver	247	170	70.0
Gastritis	213	111	52.0
Cancer of stomach	108	77	71.3
Esophagitis	104	62	60.0
Pernicious anemia	22	22	100.0
Achlorhydria	7	7	100.0
Total	1,742		

ACHLORHYDRIA, CHRONIC GASTRITIS AND GASTRIC CANCER

The incidence of *achlorydria* increases with advancing age, and it has been suggested that this may be a forerunner of other gastric and systemic diseases.

In a previous group of 1,258 patients in whom we performed gastric analysis (using histamine) as a screening test for gastric cancer, there was an increased incidence of achlorhydria and hypochlorhydria ranging from 13 per cent in the

TABLE 3

Incidence of Gastric Acidity Levels by Age Decades in 1,258 Subjects

Age Decade	No. of Patients Examined	Achlorhydria		Acidity Less than 30 Clinical Units		Acidity More than 30 Clinical Units	
		No.	Per cent	No.	Per cent	No.	Per cent
15–20	9	1	11.2	0	0	8	88.8
21–30	101	1	1.0	11	10.8	89	88.2
31–40	245	19	7.8	16	6.5	210	85.7
41–50	366	32	8.7	19	5.3	315	86.0
51–60	308	40	13.0	26	8.5	242	78.5
61–70	165	32	19.2	14	8.4	119	72.4
71–80	58	12	20.6	7	12.0	39	67.4
81–90	6	2	33.0	1	17.0	3	50.0
Totals	1,258	139	11.0	94	7.4	1,025	81.6

TABLE 4

Gastric and Duodenal Lesions Found in 1,258 Persons Subjected to Gastric Analysis

Lesion	*Group A* (no free acid) [139 cases (11%)]	*Group B* (acidity below 30°) [94 cases (7.4%)]	*Group C* (acidity above 30°) [1,025 cases (81.6%)]	Total [1,258 cases (100%)]
Gastric Lesions				
Chronic gastritis	32	13	8	53
Atrophic	[24]	[8]	[4]	[36]
Hypertrophic	[1]	[1]	[3]	[5]
Superficial	[7]	[4]	[1]	[12]
Cancer	14	1	4	19
Hiatus hernia	7	5	9	21
Polyp	5	1	0	6
Gastric ulcer	0	1	9	10
	58	*21*	*30*	*109*
Duodenal Lesions				
Duodenal ulcer	0	5	9	14
Duodenal diverticulum	0	1	1	2
	0	*6*	*10*	*16*

fifth decade to 33 per cent in the eighth decade (2). The data shown in Table 3 were obtained on patients about equally distributed in regard to sex. It has been shown (3) that when the volume of gastric secretion is considered, the total acid secreted (volume × acid) decreases with aging to the same degree in both sexes, but when acidity alone is considered the decrease is noted only in the males. It has therefore been suggested that this process may be related to hereditary

factors rather than to aging, and that the achlorhydria results from a "physiologic" involution which becomes manifest first in those persons who are endowed constitutionally with a less responsive and a more vulnerable gastric secretory mechanism. The significance of the development of achlorhydria remains to be established. However, the diseases shown in Table 4 to be so closely associated with achylia are almost exclusively found in patients of advanced years.

Twenty-four of the 36 patients with *atrophic gastritis* fell in the achlorhydric group. Although a significant number (12 patients) had free acid (Table 4), the majority were asymptomatic. Atrophy was demonstrated in all of these 24 patients by gastroscopy, and in 22 of them by gastroscopic biopsy. The gastroscopic appearance was characterized by thinning and pallor of the mucosa with a reduction in the size and number of rugae. Several small branching vessels were present in irregular patches but mostly in the fundus. There were small irregular areas of recent submucosal hemorrhage and older ecchymoses. The changes involved the body of the stomach predominantly—rarely the antrum. The histologic picture (biopsy) of chronic atrophic gastritis showed lymphoid collections in the mucosa, irregularity, fibrosis and thickening of the muscularis mucosa, loss of the characteristic gastric glands with their chief and parietal cells, and a transformation of the remaining mucosa into mucosa of the intestinal type.

Most pathologists agree that the histologic appearance of the human stomach undergoes profound change with aging. The various alterations grouped under the term atrophic gastritis are entirely absent in the fetal stomach and only begin to appear with significant frequency in the third and fourth decades of life. They are present in varying degrees in over 80 per cent of "normal" persons from the fifth decade on. These changes include a decrease in mucosal thickness, an increase in leukocytic infiltration and lymphoid aggregates, intestinal metaplasia, and pyloric-gland heterotopia. It is reasonable to assume that these alterations are the basis for the decline in gastric secretion which occurs with advancing age (3).

Results of experimental studies in animals indicate that persons with achlorhydria should be more disposed to gastro-intestinal infections because of loss of the "sterilizing" action of the gastric acid. They should be more prone to the

TABLE 5

Number of Deaths among 151 Patients with Ulcer Treated Medically or Surgically

Type of Ulcer	Total No. of Patients Treated	Medicaal		Surgical	
		No. of patients treated	No. of deaths	No. of patients treated	No. of deaths
Duodenal	112	68	10	44	8
Gastric	28	16	6	12	1
Marginal	11	8	1	3	0
Total	151	92	17	59	9

development of hypochromic microcytic anemia because of the role that gastric acid plays in the absorption of iron. In man achlorhydria occurs almost constantly in association with pernicious anemia and subacute combined degeneration of the spinal cord, frequently in association with hypochromic microcytic anemia, and sometimes in association with diarrhea and vague digestive complaints. Most observers now agree that the incidence of pernicious anemia, like that of achlorhydria, increases with aging. It appears that a decline or disappearance of "the intrinsic factor" may occur with advancing age, but whether the decline is due to aging *per se* or is related directly to the causes of achlorhydria or gastritis is uncertain.

Carcinoma of the stomach, like most other cancers, shows an increased incidence in older patients. The relationship of atrophic gastritis to gastric cancer has been widely studied. Konjetzny (4) has been the keenest proponent of atrophic gastritis as a frequent precursor of gastric cancer. Schindler (5) has also favored this view, and the studies of Brown (6), Orator (7) and others have demonstrated the frequent association of atrophic gastritis and gastric cancer. This relationship is also suggested by the frequency with which pernicious anemia is complicated by gastric cancer. Atrophic gastritis is now recognized as a regular accompaniment of pernicious anemia, and Magnus and Ungley (8) have pointed out that the atrophy is not patchy in pernicious anemia, as in most idiopathic achlorhydrias, but is diffuse and involves all layers of the gastric wall,

TABLE 6

Factors Contributing to Death in Cases of Ulcer Treated Medically Versus Those Treated Surgically

	Type of Ulcer		
	Duodenal	Gastric	Marginal
Cases treated medically			
Delay	2		
Myocardial infarction	2	1	
Cirrhosis with perforation	2	1	
Uremia	2	1	1
Cardiovascular accident	1		
Raynaud's disease (cortisone given)	1		
Cirrhosis (corticotropin given)		1	
Congestive heart failure		2	
Cases treated surgically			
Emergency:			
Open duodenal stump	1		
Pancreatitis	1		
Lymphosarcoma (corticotropin given)	1		
Dermatomyositis (corticotropin & cortisone given)	1		
Interval:			
Postoperative bleeding	2		
Delay	2		
Congestive heart failure		1	

particularly the body and fundus. Kaplan and Riegler (9) have stated that the incidence of gastric cancer in patients dying of pernicious anemia is 12.3 per cent or three times the expected necropsy incidence of gastric cancer in patients of the same age group.

PEPTIC ULCER

Although peptic ulcer remains predominantly a disease of the third and fourth decades of life, there has been an increase in incidence in older patients within the past few years. It is in the patient over 50 that serious complications are prone to develop, particularly in the patient with massive bleeding from a peptic ulcer. In our series of 151 cases of ulcer (Table 5), 92 were treated only medically (with a mortality rate of 18.3 per cent), and 59 were treated surgically (with a mortality rate of 15.2 per cent) (10). These mortality rates are high but it should be noted that all but 2 patients were beyond the fifth decade of life and had suffered from massive continued or recurrent bleeding in each instance in which death occurred. It should also be noted (Table 6) that many of the patients had complications in other body systems including a cerebrovascular accident, coronary occlusion, uremia and cirrhosis of the liver—all diseases of advanced age.

CONCLUSIONS

Symptoms referable to the gastro-intestinal tract occur with great frequency in older patients. After the age of 50 there is a distinct increase in organic disturbances such as hiatal hernia, achlorhydria, gastritis, gastric cancer, gastric polyp, and pernicious anemia. There is also an increased mortality rate from peptic ulcer complicated by massive bleeding. Associated disease in other body systems is a prominent finding.

When the evaluation of intestinal aging is restricted to the esophagus, stomach and small bowel, there is almost no evidence of a wearing-out process such as is demonstrable in certain other body systems. The exception is the progressively increased incidence of achlorhydria with aging. The relationship of atrophic gastritis, pernicious anemia, and gastric cancer to achlorhydria is discussed.

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GERIATRIC ASPECTS OF RECTAL DISEASES*

JOSEPH FRANKLIN MONTAGUE, M.D., F.I.C.S., F.A.G.S.†

New York, N. Y.

In many of the clinical conditions which we as physicians and surgeons are privileged to observe, there are certain hidden factors, the significance of which may be overlooked or unrecognized unless we are alert to the possibility of their existence and aware of their importance. For instance, consider the truly great influence the aging process has in the production and course of certain proctologic diseases.

Outstanding examples of proctologic conditions that can frequently be attributed to changes incident to the aging process are rectal prolapse, diverticulosis of the colon, polyposis of the lower bowel, carcinoma, colitis, pruritus ani, and hemorrhoids.

To illustrate more specifically the manner in which the aging process is productive of rectal ailments, the pathologic-physiologic causes of hemorrhoid formation are presented.

HEMORRHOIDS

Primarily the formation of hemorrhoids is dependent upon the existence of a structural weakness in the walls of the veins caused by a loss of tone of the muscle fibers in the venous wall and in the levator ani.

The wall of the hemorrhoidal vein, weakened by lack of normal tonicity, readily yields to any increase of pressure within the hemorrhoidal area. It responds by elongation, dilation and thinning of the vein wall, with subsequent swelling.

The increased size of the vein makes it tortuous and large, causing it to protrude into the rectal lumen, where it is subject to additional trauma. This gives rise to another clinical sign—the sense of rectal fullness or weight.

The levator ani muscles cease protecting the area from intra-abdominal pressure, become less efficient in defecation and tend to permit prolapse of the hemorrhoids.

Perhaps, the question arises as to *why* the smooth muscle, of which the middle coat of the vein wall is composed, should show degenerative changes. There is nothing extraordinary in the process. In fact it is rather illogical that the clinical mind, which has accepted the idea of senile arteriosclerosis so wholeheartedly, apparently has never suspected that changes may occur in the venous side of the vascular tree. Nowadays aging has come to be regarded as an important problem. Vascular diseases are predominantly "the problem within the problem," and the walls of the veins are just as much affected by the progressive alteration of vital function as are those of the arteries.

* Paper read at The University of Bologna, Italy, May 26, 1960.

† *Address:* 104 East 40th Street, New York 16, N. Y.

Statistics show that the greatest incidence of hemorrhoids is in the fourth and fifth decades of life, when stress and strain are most severe and muscular tone normally diminishes. It is at this time that the first indications of oncoming senility appear. Is it not logical to assume that there may be a relation between the two conditions? It is known that loss of muscle tone due to failing gonadal secretion is a definite indication of the progressive changes that terminate in senility. A diminution in pituitary hormone accelerates these processes.

Moreover, smooth muscle throughout the body derives its innervation from the sympathetic nervous system; therefore the muscle cells in the walls of the veins are so innervated. The pituitary hormone is the one that controls, or at least exerts the greatest effect on the sympathetic nervous system. The failure in quantity or quality of this hormone determines directly or indirectly the normality or subnormality of the muscular tone of the veins.

If the foregoing statements are true of the muscular tissue scattered throughout the wall of the hemorrhoidal veins, they are equally true with regard to the muscle fibers of the levator ani. Experimental workers in the field of endocrinology have long since discovered that the levator ani is particularly sensitive to the effects of androgenic substances. For years they have used these specific muscles in the rat for making androgenic assays. An unrecognized fact, of great importance in the causation of hemorrhoids, is loss of tone in the levator ani. Their normal function is to protect the anal and rectal structures from the pressure of the abdominal viscera. Thus progressive failure of that function brings to bear pressure factors which, when added to the intrinsic weakening of the venous walls, induce hemorrhoid formation.

Senility is by no means synonymous with age. It can occur prematurely; on the other hand, it can be postponed to some degree. The key to the situation is definitely connected with the glands of internal secretion. Whatever affects them affects, in turn, the rest of the body tissues. Chronic intoxication, faulty nutrition, anemia, or mechanical interference with a specific endocrine organ all have their influence upon the secretion of that gland. Endocrine imbalance may have the same effect. Atony of smooth muscle is directly proportional to the diminution in secretion of the gonads, the pars nervosa of the pituitary gland and possibly of other glands of internal secretion.

Hemorrhoids occur with greater frequency in the later decades of life, in correlation with the normal decrease in muscle tone that occurs as a result of the normal decrease in gonadal and pituitary hormones. Hemorrhoids in younger persons are also in accordance with this theory; they are a sign of "senile" change. Thus hemorrhoids are a geriatric problem *at any age*.

COLITIS

Age has a strong influence on the course of colitis. In people past the age of 50, ulcerative colitis is a more serious problem than in youth, and the severity of the condition bears a direct relation to the age at which it first developed. Its rapidly progressive nature (in some cases, explosive) frequently necessitates colectomy within a year or two—a relatively short time. An outstanding feature

of the condition in elderly people is the pronounced tendency to lose control of the anal sphincter.

The older the patient at the time of onset, the more serious the course is likely to be. The diarrhea is more severe and prolonged, resulting in marked emaciation and loss of strength and weight. Bowel hemorrhage is more often the leading symptom in elderly patients than in younger ones, and the loss of blood is made more serious by the impaired hematopoietic powers of the elderly person. Ulcerations of the rectum and sigmoid are more extensive in elderly persons than in younger people, and the healing process is more often complicated by stenosis resulting in partial obstruction. Elderly patients with colitis are more likely to respond to steroid therapy by a sudden extension of the ulcerations, and even necrosis of the bowel wall.

Senile tissues are ill equipped to combat a severe process such as ulcerative colitis. Therefore corticosteroid therapy, which theoretically is the perfect answer to reduced hormone production on the part of the patient, should be employed with caution in elderly patients because of the tendency to induce perforation and hemorrhage.

COMMENT

It should be emphasized that many proctologic disorders are due to the inescapable effects of time. A thorough rectal and sigmoidoscopic examination of every patient, regardless of whether or not complaints are referable to proctologic areas, will serve the good purpose of early detection of these conditions if they exist. The results of such examination may lead to early treatment, which is the best hope for satisfactory management, and in the case of cancer is the only chance for cure. Involution or degeneration of various tissues of the body may occur as a senile process *at any age*, well in advance of what is commonly considered to be old age. Thus our attention and efforts should be formulated along broader lines so as to supplement the specific treatment of the demonstrable diseases in the field of proctology.

Poor nutrition and muscle tone are at the basis of many proctologic ailments. Therefore the total health of the patient—his nutritional and functional well-being—are of prime importance in the management of these disorders.

THE IDEA OF A HOME FOR THE AGED: A RE-APPRAISAL

WILLIAM ALDERS, M.A.*

Bronx, New York

Whether or not it is fortunate that many of us will grow old depends upon the point of view. Although most of us want to achieve an old age, we are frequently unaware of the drawbacks. When such thoughts do occur to us, it is likely that we will apply them to "the other" person. Thus if we cannot project ourselves into the feeling of "For Whom the Bell Tolls," we shall never grasp in depth the troubles of the aged, nor feel them within ourselves. We shall never understand the sufferings of the other person who is old, or what he is going through in terms of psychologic stress, physical deterioration, and often severe pain. Perhaps it would be too much to expect.

But we should know that age never reduces one to a status less than that of a human being. An old person has given his service to the community, while growing old. He has worked in productive fields, supported a family, and helped others. He was an integral part of the society in which he lived. Now he is a burden upon that same society which he helped to mould, and whose help he needs. Often for shame alone, we listen to his call, or to the call of those who have long known about the unfilled needs of the increasing numbers of the aged.

THE INSTITUTION

Long before the problem became acute, sympathetic persons began organizing what seemed to them to be a solution for the hiatus in the lives of the aged, namely, special homes. Little did they know that the end of their good intentions was a setting apart and a demeaning of the old person, for having had the *fortune* to grow old. This person was removed from the life of the community by being assigned to an institution. He became a thing apart from the social and political life of his time. But he was considered to have been set in a comfortable groove, away from all the malfunctions of society. He would not have to struggle any longer among the cold masses, where his chances were negligible.

Loss of privacy

Little was it realized that this helping hand was also helping to strip the person of one of the most precious gifts bestowed by our civilization—individuality. By now there is no need to enter into a description of the word's meaning, but privacy is an integral part of it. Loss of privacy first occurs at the portals of the institution, and once inside, the resident "wears" it like a badge throughout his institutional career. There are people who like to see their names written across the sky and who do not mind pulling down the walls of their dwellings (figura-

* Executive Director, United Odd Fellows Home and Orphanage Association of the State of New York.

Address: 1072 Havemeyer Avenue, Bronx 62, New York.

tively speaking) in order that outsiders may peer in; such people will expose even intimate or delicate situations to public view, in their perverted desire to be noticed. But these are exceptions. The rest want to know themselves, and have others know them as a particular star—even if only one in a sea of stars. And as this kind of star, a person has his own majesty and honor.

Submersion of the ego

Would it be preferable to eliminate the source of the evil, which is a sociologic throw-back, by demolishing the institution known as the old-age home? If we are still groping for other organizational methods of assisting the old person in his period of helplessness, should we look in other directions? The problem is doubtless enveloped in a thick fog, which we might disperse by looking at the core of the matter—the need of the aged person to be considered as an individual. The need of recognition as such remains with him while he has life and hope, for then he is himself, a person, a "star," and acknowledged in his community. We must concede that almost everyone loves his own home. It is his shell, his palace, his museum and his redoubt. If one person can be found who loves the institution, then he will be the exception to the rule. The institution is an unloved entity that remains as a leftover from centuries long gone. The aged person, forced to accept the institution as the last of his residences, does so with many mixed and unblessed feelings.

Bigness can be a fearsome thing, appearing in the shape of a gargantuan building with a giant maw to swallow up our personality, our separateness and our greatness. The sensitive person who has been drawn in will find himself an aimless being left to grope for a way of replacing the lost treasure of his past—hopelessly. Once inside, the ego of the resident will sink into a boundless, selfless void, where he will leave no trail of his former importance. He will be counted, rather than identified; and here he will be part of an amorphous mass. If this is a lugubrious and lamentable picture, then we cannot boast of having advanced very far in our efforts on behalf of the elderly, for whom we have provided these institutions. Up to now our achievement consists of the establishment of a situation in which there is a choice of evils; but the evil inherent in institutional life is still with us and probably always will be.

The injury sustained by the ego on admission is probably less severe than that which follows. The instincts of pride and dignity are invaded by those whose interests do not depend upon a blood relationship, but generally upon a regulated attitude toward a mass. Although a few people lack the self-respect which spells humiliation, in this situation, most of them are mortified. Some persons have the means to purchase privacy, and do not need to abase themselves. Thus we are responsible for making privacy a purchasable commodity, and for equating the dignity of an individual to the size of his purse. If we have the courage to admit our shortcoming, we shall have taken the first step in opening a road to new horizons.

There are some among our aged who will resist the "opportunity" that institutional care offers them, even in their troubled and helpless infirmity. They

will endure physical suffering by choice, rather than accept charity on such terms. However, in situations where the less strong will yield to the beckoning of the institution, we often find the origins of frustrations, unsocial behavior, and psychoses.

If we follow a prospective resident along the line toward admission, we shall find him, in the process, being typed, categorized, and classified. Almost anyone will resent labeling, like a can of beans. ready for disposition on a shelf. But the success of his application will depend upon answers to many questions: What are his ailments, his faults, deficiencies, failures and lacks? His past and possible future achievements are of secondary, if any, interest. Having met all arbitrary tests in line with policy, he is led inside and assigned to a bed which he can call his "own." With this bed goes a modicum of space where he can keep his personal belongings, which consist of no more than the absolute day-to-day necessities. Of the accounterments of his former personal majesty he must be denuded. Thus he is left to join the ranks of men who are forgotten after their days of glory are ended. Taking his farewell of the outside world, the new resident enters upon a communal, lusterless, impersonal life.

There are exceptions among homes for the aged where this censure will not wholly apply. In some, there is a conscious effort to overcome this static atmosphere which envelops the lives of their residents. It is also true that some of the residents had led "herd" lives, notable for the absence of precious individuality. Nor is living one's own life in one's own home synonymous with independent thought and action, on all occasions. But every man, with few exceptions, looks upon his home as his castle. There he is somebody. There he can speak of "Me" and "Mine," and sense the exaltation of his ego. There he looks upon himself as a name, a being that is part of an integrated whole, a meaning to others as well as to himself. Whatever his part, he there feels equal to the whole and may, in his little self, even pretend to represent it. Certainly his home is where he is farthest from the *submersion which is the institution.*

Let us look at the resident who is of rugged character, and will not readily accept oblivion as his living fate. He will stand up for a time to boredom, to dull days, and to a dark future. He will cling to the shadow of his former self. He will try to see, in the guise of people, those around him who no longer claim themselves for their own, having lost the power of response. Frequently he will find himself alone, unknown and unregarded. Soon he may become a non-entity, even to himself. He is in danger of losing hope at a critical point of his sojourn in the institution. He may even lose his desire to live, so that he will find himself reconciled to what will therefore come sooner. He will get farther and farther away from those who used to share his joys and sorrows. He will find himself even more alone, because he is now among many like himself, who have come late into his life and who can have no future either with him or without him.

RE-APPRAISAL

If to the optimists who are working in the arena of geriatric care this is a somber and bleak picture, we hope that the few bright rays of sunshine which sometimes

suffuse it will not blind them to the basic truth. Only appropriate action, following the recognition of this truth, will make it possible for the old person to live out his years under less discouraging circumstances. Some of that excellent band of workers who spend their lives thinking about this problem, are working to make life more worthwhile for the aged. Thus we see an expansion of recreational, occupational and self-help programs, in the search for improvement. Under great handicaps these workers continue to grope for remedies on behalf of the aged, in order to bring them back into focus, to restore them to a more useful place in society, and to confer on them a sense of belonging. What is needed is *a return to fundamentals*, and a re-appraisal of the home, as well as of the institution.

If we carry our criticism still further, we shall see that the institution, once our vision is cleared, bears an uncomfortable resemblance to a camp for displaced persons. The euphemism of "Home" cannot restore the old person to the place where he belongs, nor adequately substitute for it. This does not mean that a determined effort should not be made to approximate his home in instances in which the institution, after analysis, is found to be the lesser of two evils. *But under no circumstances should an institution take the first place in our thinking.* There is an intensive job of social service to be done, which the more thoughtfully performed, will the better assist the aged one in his dependency. The *sick* aged are more properly *subjects for a general hospital, where they have a right to share with younger patients in the distribution of medical care.*

Re-appraisal of the institution must be dependent upon re-appraisal of the homes from which it draws its residents. Whenever the problem of the aged person can be solved in his own home, either directly or by subsidy, this should be the chosen method. Apart from the immediate humane considerations, we would gain in (a) huge savings of money, (b) a conservation of beds, and (c) the preservation of home and family life. It is much less expensive to the community to subsidize the home than to construct and maintain the institution. It costs comparatively little to supervise, assist and aid the aged person in his home, and it leaves more room in the institution for those who have been deprived of choice. It provides continuity of care of the best kind. Home-care programs have proved themselves over the last decade. Apartment-house projects are an attempt at approximation to the home, but are still institutional in their nature and substance. The institution, as an unwholesome substitute generally, should strive to make its existence unnecessary. However, regardless of where the old person should spend his latter years, the problem remains as to how to give him the individual attention by which he will continue to know that he is still a man. Offhand diagnoses and prognoses will not help us to find the answers when we question and seek a re-appraisal of the institution.

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COMMON ORTHOPEDIC PROBLEMS OF THE AGED

GEORGE J. SEAMAN, M.D.* AND JULIUS A. SCOTTI, R.P.T.

Menorah Home and Hospital for the Aged, Brooklyn, N. Y.

The frequency of orthopedic complaints in the geriatric population is extremely high. The material for this presentation was collected from The Menorah Home and Hospital for the Aged, an institution of 420 people, all of whom are past 65 years of age; about 250 are in the hospital and infirmary section and 170 in the ambulatory resident section. When necessary, the data have been supplemented by case material from private practice and from other hospitals and clinics.

Conditions which are common in the aged or for which treatment is different in the aged will be discussed.

DISORDERS COMMONLY OBSERVED IN THE AGED

Neck pain with radiation to the upper extremity

The two most common causes for this type of neck pain are cervical osteoarthritis and trapezius myositis The extent and severity of the *cervical arthritis*, as seen on x-ray examination are not closely correlated with the severity of the symptoms; thus x-ray evidence of arthritis by no means assures that the symptoms are due to this disease process. The presence of anterior osteophytes, in itself, is not of great significance. However, the demonstration (on oblique views) of foraminal compression by osteophytic spurs may be directly correlated with the symptoms. There is a decrease in the range of neck motion, but this must be interpreted cautiously.

The diagnostic features of *trapezius myositis* are: reproduction of the pain by resisted abduction of the arms or resisted elevation of the lateral end of the clavicle (1). There is no pain on passive motion of the shoulder or neck, unless the motion is of such a degree as to stretch the trapezius muscle.

In treating cervical osteoarthritis, the use of the Seaman cervical collar (2) is recommended. This is a thermostatically controlled heating pad shaped like the Thomas collar, which gives both heat and support to the neck. It is sometimes supplemented by cervical traction, galvanism and administration of salicylates. For treatment of trapezius myositis, ethyl chloride sprays applied locally are very effective. An elastic attachment which pulls the shoulders backward is often applied; it can be found in most surgical supply stores and is called a shoulder retraction bracelet. When these measures have not succeeded completely in relieving the pain, iontophoresis, using Imadyl unction, is added. The results of treatment are generally good, but the symptoms tend to recur when

* Director of Orthopedic Surgery, Menorah Home and Hospital for the Aged; Associate in Orthopedic Surgery, New York Medical College, New York City.

Address: 99 Lafayette Avenue, Brooklyn 17, New York.

the treatment is stopped. Fortunately, they are then readily controlled by home measures and self-treatment.

Shoulder pain

If the onset of shoulder pain occurs after the age of 60, the diagnosis is much more likely non-calcific *bursitis* than calcific bursitis. Essential to the diagnosis of bursitis is the presence of pain on motion of the shoulder, with little or no pain on muscle contraction only (in contrast to trapezius myositis). Shoulder bursitis, whether calcific or not, may be treated by local injection of hydrocortisone or one of its derivatives into the irritated area. When the pain is relieved, a gentle exercise program is instituted; if this is not done, a "frozen shoulder" will develop. In addition, ethyl chloride sprays and galvanic current may be used. Noncalcific bursitis does not seem to respond as well as calcific bursitis.

Many names are given to the attritional changes which take place in the aging shoulder. However, the severity of these alterations, as seen at autopsy, is poorly correlated with the severity of symptoms. Most of the changes are asymptomatic (3).

Adduction-internal rotation contractures of the shoulder develop rapidly in patients with hemiplegia, particularly when they sit for long periods. Muscle spasm, which occurs late in the course of the disease, is of varying severity. The less severe contractures can be overcome by a judicious exercise program, but those involving severe spasm will not respond, particularly if there is a tightly clenched hand and a flexed elbow. The prognosis for recovery of function in the afflicted upper extremity is so poor that the time should be spent trying to improve the dexterity of the remaining good upper extremity. We have not seen any worthwhile improvement from surgical operations on the extremely spastic upper extremity.

Not infrequently, extremely severe pain develops in a hemiplegic upper extremity. When caused by *subluxation of the shoulder joint*, a sling is helpful, although shoulder fusion may become necessary. If a sling is used, it should not be put around the neck; it can be fixed over the affected shoulder and back of the chest. In cases of hemiplegic subluxation of the shoulder, surging faradic stimulation of the deltoid muscle is beneficial. In hemiplegic patients, severe pain in the upper extremity may be of the causalgic type—so-called *thalamic pain*—probably due to thalamic hemorrhage. Management is extremely difficult, as there is a high incidence of associated emotional instability. Our Director of Neuropsychiatry, Dr. E. L. Reder, uses trihexyphenyl hydrochloride (Artane) as in the treatment of Parkinson's disease, with fairly good results.

Hand and finger pain

Heberden's nodes of osteoarthritis, rheumatoid arthritis or mixed arthritis may cause hand and finger pain. In addition to aspirin or its derivatives, paraffin baths, whirlpool baths or galvanism may be used in treatment; Imadyl unction is a good vehicle for iontophoresis. The baths can be carried out at home. We

have recently devised a special heating pad, shaped like a mitten, into which the hand can be inserted; initial results have been quite good, but further evaluation is necessary.

Stenosing tenosynovitis of the fingers or the radial styloid usually responds well to local injections of hydrocortisone. However, there is a high incidence of spontaneous recovery, particularly in the senior golfer. If symptoms persist, excision of the tendon sheath is necessary.

Dorsal spine pain

Senile kyphosis is also almost universal. It is due to such conditions as osteoporosis with vertebral wedging, compression fractures, or narrowing of the anterior portion of the intervertebral discs—in varying combinations. The correlation between symptoms and x-ray findings is very poor.

If the pain is in the *upper or middle section* of the dorsal spine, the shoulder elastic retraction bracelet is helpful. In men, relief of symptoms can be attained by the use of special suspenders; the rear loops are attached to the trousers, the suspenders are brought over the shoulders, and the front loops are brought under the axillae and tied together or attached to the rear buttons. This serves to retract the shoulders passively and tends to straighten the dorsal spine, relieving some of the tension on the posterior structures. The suspenders do not hold the trousers up; a belt is necessary. The foregoing measures should be used if examination reveals that passive retraction of the shoulders produces relief of pain. If passive shoulder retraction does not produce relief, further investigation should be conducted to see if there is a visceral cause for the symptoms.

For *lower* dorsal spine pain in women, a snug, long-line brassiere usually provides relief; in men, a snug vest serves the same purpose. For both upper and lower dorsal spine pain, physical therapy (particularly diathermy and galvanism) is helpful. When symptoms have been relieved, spinal extension exercises will serve to improve muscle tone and thus prevent recurrences. However, aged patients rarely perform the prescribed exercises, unless they are in an institutional atmosphere where these exercises can be supervised regularly.

The combined estrogen-androgen treatment of *osteoporosis* will relieve the symptoms (4) even though the x-ray appearance is not changed. The supplemental use of calcium and vitamin D for osteoporosis is not warranted and may do harm by causing calcium deposition in the soft tissues or the kidney.

A condition due to irritation, arthritis or other changes in the dorso-lumbar region (*dorso-lumbar syndrome*) (5) is not peculiar to the aged and is extremely difficult to treat. It is manifested by severe limitation of motion of the spine, severe pain on motion, and a zone of hyperesthesia in the D12-L1 zone. The most characteristic physical finding is the reproduction of pain on twisting; this test for pain must be performed when the patient is seated. Paravertebral block provides the best relief of pain, but the results are erratic. The block is sometimes ineffective, but in other patients one injection may result in fairly long-term relief. The condition responds poorly to diathermy, galvanism or infrared therapy, except for temporary palliative benefit. If a corset is to be used (and it is fre-

quently necessary) it must extend over the shoulders to provide some immobilization of the dorso-lumbar spine. Corset fitting is extremely difficult, because of the hyperesthesia of the abdominal wall.

Low back pain is not as common in aged patients as in younger, more active patients. The reason is probably decreased activity. Herniated disc is extremely rare in the aged. The most frequent cause of low back pain in the aged is osteoarthritis of the lumbar spine, but the correlation between the severity of the x-ray changes and the severity of the pain is very poor. Great relief is usually obtained with a lightweight corset, the use of a firm mattress or bed board, and administration of salicylates. Diathermy is often necessary, particularly if there is radicular pain. The results of treatment are good.

Scoliosis which increases or has its onset in old age is by no means rare, and it can be very painful. The etiology is the same as for senile kyphosis of the dorsal spine—vertebral compression, narrowing of the discs, and small compression fractures. The treatment is the same as for osteoarthritis of the lumbar spine. However, the response to treatment is not as good, because in scoliosis of the aged there is frequently compression of the nerve roots, a condition which is difficult to relieve.

The onset of back pain in a patient over 45 should always arouse suspicion of metastatic carcinoma. The probability of this diagnosis is greater if the pain is not relieved by rest and is worse at night, or if compression of the vertebral body (when present) is limited to a single vertebra. If both anterior and posterior borders of the vertebral body are compressed, the likelihood that the lesion is metastatic carcinoma is extremely high.

Hip pain

Osteoarthritis of the hip (malum coxae senilis) is fairly common and is often unilateral. It is the result of some old mechanical derangement of the hip in childhood or adolescence, such as mild congenital dysplasia, slipped epiphysis or osteochondritis. If the symptoms are sufficiently severe and the patient's general condition permits, an operation should be performed. The choice of operation is wide—arthrodesis, cup arthroplasty, prosthetic replacement of the femoral head, or osteotomy. When the symptoms are less severe or when there is a medical condition which does not permit operation, conservative therapy should be attempted. A reduction in body weight is mandatory and a reduction in activity (particularly stair climbing) is important. The use of gum-soled shoes is helpful. Physical therapy is of no particular benefit, nor is the intra-articular injection of steroids. If the foregoing measures do not help, a period of complete bed rest may provide relief. Traction at night is recommended; with the aid of sponge rubber and an elastic bandage, it is not difficult to apply the five-pound weight.

Trochanteric bursitis is not as common as shoulder bursitis in the aged, and again the noncalcified form is more frequently observed. The treatment is the same as for shoulder bursitis—local injection of corticosteroids, ethyl chloride sprays and galvanism.

The late complications of *hip fractures* are extremely varied. They include shortening and external rotation of the lower extremity with pain and limp, extrusion of the surgical nail with resulting subcutaneous irritation, intrusion of the surgical nail with resulting severe pain on motion of the hip, aseptic necrosis, osteoarthritis, and non-union. Each of these complications is a separate problem; the decision as to whether or not to operate and the choice of operation depend on the general condition of the patient. Malunion with shortening and external rotation can be helped by the use of a shoe-lift (not as much lift as the amount of shortening), a cane, and intensive exercises designed to achieve the best possible muscle power, particularly in the quadriceps, gluteus medius and gluteus maximus. Symptomatic intrusion or extrusion of the surgical nail demands extraction of the nail, but only if union has already taken place; if not, the patient must continue to suffer from the symptoms until there is union. Aseptic necrosis can be treated in the same manner as osteoarthritis, but the results of nonoperative treatment are not good. Not every case of non-union of the femoral neck demands operation. In some patients, the medical condition does not permit it. In others, it is possible to achieve limping but painless ambulation with the use of a cane, and operation is not necessary. The choice of operation depends somewhat upon the physical vigor of the patient. At present, the most highly favored procedure is femoral-head prosthesis. The results are not as good as when applied to fresh fractures. A perfectly functioning hip with a prosthesis is extremely rare (in the sense that it is extremely rare to see a perfectly functioning set of artificial teeth) but, in the absence of technical complications, the results are satisfactory to the patients, who generally are limited in activity.

Thigh pain

Meralgia paraesthetica—neuralgia of the lateral cutaneous nerve of the thigh—is not uncommon in aged men. It is frequently caused by irritation from a hernia truss; proper fitting of the truss provides relief. In other cases, injection of procaine or hydrocortisone into the nerve where it crosses under or partially through the inguinal ligament (about 1 inch medial to the anterior superior spine) gives excellent results.

Another common cause of pain in the thigh is *osteoarthritis of the lumbar spine* in obese patients. Loss of weight and the use of a corset are beneficial.

Knee pain

Disorders of the knee are very common, particularly in overweight aged women. The high incidence of *knock knees* and *bow legs* in these patients is striking. Osteoarthritis, tender popliteal fat pads, ligamentous strains, and bursitis are the usual causes of *knee pain* in the aged. Knock knees or bow legs cannot be corrected, but a wedge placed on the medial side of the shoe in the case of knock knees and on the lateral side of the shoe in the case of bow legs will relieve some of the ligamentous strain. Ethyl chloride sprays, galvanism, injection of hydrocortisone, elastic bandages and local heat are all beneficial. *Osteoarthritis* of the knees can be treated by quadriceps progressive resistance exercises to prevent

recurrences, but these exercises can be started only when the symptoms are subsiding.

Flexion contractures of the knee, due to old hemiplegia, rheumatoid arthritis or osteoarthritis can be straightened by casts with Forrester hinges. Quadriceps exercises and stretching of the hamstrings preceded by heat to the knee will sometimes be sufficient. A brace may be necessary to prevent recurrences. If this conservative treatment is ineffective, operation should be performed to divide the posterior structures of the knee. By surgical means, the knee can be straightened, but it requires the utmost co-operation on the part of the patient to undertake the knee-strengthening exercises that are necessary for restoration of gait. Usually the operation is successful in straightening the knee, but the patient cannot walk because of lack of motor power in the knee muscles.

Leg pain

One of the most difficult diagnostic and therapeutic problems in orthopedic conditions in the aged is pain in the legs. Usually no local signs are evident upon which to base a diagnosis of a local lesion—that is, there is no swelling, deformity, atrophy, limitation of motion, loss of strength, pain on resisted motion, or pain on any motion; and the reflexes, sensation, motor power, skin color, hair growth, and peripheral pulsation are normal. There is no abnormal coloring of the skin either in the elevated or the dependent position. Some of these signs may be present and in some cases add up to a specific diagnosis, but in most instances they provide no clue. For lack of a better label, the condition just described has been reported as "radiculitis" (despite the lack of findings in the lower back) or "neuritis" (despite the normal reflexes). We are not in a position to assign any better diagnosis, and for purposes of classification have called it "*leg pain, cause unknown.*" We have observed that peripheral vasodilators, used judiciously in the aged, will produce relief of this pain in chronic cases. Whatever the nature of the condition (it is probably several different entities), we have not obtained good results with vitamin-B complex and its purified forms or with most forms of physical therapy. Galvanism or ethyl chloride sprays or sometimes a whirlpool bath will sometimes help more than temporarily. However, the syndrome should be classified presumptively on a vascular basis. When there is a history of the condition becoming worse with warm baths or worse after exposure to diathermy, peripheral vasodilators may be prescribed even if skin temperatures and oscillometric readings are normal.

An extremely frequent complaint of the aged is called (for lack of a better name) *restless legs*. Painful muscle cramps awaken the patient during the night, but a small amount of walking relieves the cramps. The frequency is variable. Physical examination does not reveal the cause. Quinine sulfate (5 grains twice a day at 4:00 p.m. and 8:00 p.m.) relieves the symptoms; when relief is obtained (in three to six days) the dose is reduced gradually. Surprisingly, the cramps usually do not recur when the medication is stopped. Other medications have been advised, *e. g.*, calcium lactate, strophanthin and diphenhydramine (Benadryl), but our results have been so good with quinine it has not been necessary

to use these drugs. If the condition is persistent, the blood calcium and potassium levels should be checked.

Foot pain

In the aged, foot pain is due to such a complicated group of conditions that it cannot be covered in this presentation. A frequent cause is selective atrophy of the subcutaneous fat of the sole of the foot. This produces a burning pain and may be confused with the pain due to vitamin deficiency. The use of gum-soled shoes is of great help. *Metatarsalgia* from reversal of the anterior metatarsal arch is difficult to treat, for the aged do not tolerate well any corrective appliances inside their shoes; in fact, the pain is often increased by use of an inside metatarsal pad. Denver heels (anterior metatarsal bar), though perhaps not so logical, are usually more effective than an inside wedge. Reversal of the normal curve of the arch is usually too fixed to permit correction by less than operative means. For control of symptoms due to *flat feet*, sponge scaphoid "cookies" mounted on flexible leather can be inserted into the shoes, as in the aged metal plates are painful. For the treatment of *splay foot* (*metatarsus primus varus, bunion, hallux valgus, bunionette and reversed metatarsal arch*) if the circulation is good and the patient physically vigorous, we recommend the Joplin operation (6)—division of the adductor hallucis and tightening of the arch by a transplanted tendon. The results have been most satisfactory. The routine x-ray picture of the foot does not change after operation; however, if films are obtained during weight bearing before and after surgery, it will be seen that the metatarsal area spreads less after the operation. The patients are seeking relief of symptoms; any improvement in appearance is a secondary gain. For the treatment of splay foot in a less physically vigorous patient, we use bunion elastic traction at night (7). The apparatus pulls the big toe into the varus position; in non-rigid hallux valgus some correction results, and in both rigid and non-rigid hallux valgus there is some relief of symptoms. For splay foot in aged women, we never order heavy custom-built "orthopedic" oxfords, but rather lightweight gum-soled wedgies (sometimes adding an anterior metatarsal bar on the outside). The weight of a heavy shoe increases symptoms. No matter how strong the shoe, the shape of the foot will not be changed. For isolated hallux valgus in the aged, the measures used for the treatment of splay foot relieve the symptoms, but in some cases surgical excision of the bunion is necessary.

Certain diseases of the bones and joints

Gout, when first appearing in patients past the age of 55, often manifests itself in areas other than the big toe, namely, the hands, wrists, knees and shoulders, in that order. The big toe, however, is still the most common site, as noted in about one-third of our patients.

Multiple myeloma must be considered when there are multiple bone and joint pains, particularly diffuse chest tenderness.

Vitamin deficiencies are moderately common, particularly those involving vitamin B. Lack of vitamin B results in burning pain or paresthesia of the feet

or legs. The symptoms are not always bilateral and, if bilateral, not often symmetrical. Some cases of vitamin deficiency were originally classified as "leg pain, cause unknown" and vice versa. Changes in reflexes and sensation are present only in advanced cases. The response to treatment with vitamin B complex or the purified derivatives is slow; the use of peripheral vasodilators sometimes speeds the relief of symptoms.

Generalized osteoarthritis (true osteoarthritis, involving multiple joints) is not particularly common. Aspirin or some other salicylate is the drug of choice. Cortisone is not recommended. Phenylbutazone can be used only for short periods, when an injury has been superimposed on pre-existent arthritis.

One of the most difficult problems in treatment is the "*chronic confirmed hypersensitive arthritic.*" All joints are painful; all laboratory findings are negative or not significant; and x-ray changes are minimal and within the average for the age. The condition is really psychogenic rheumatism. In the aged, treatment is well nigh impossible. We use mild calisthenics and purposeful activity and exercises, but the results are poor.

Paget's disease of bone is observed fairly frequently, and from half to one third of the patients have pain of variable severity. Limitation of motion occurs when there has been intrusion of the femoral heads into the acetabulum (Otto pelvis). Intravenous injection of 0.1 per cent procaine (average dose, 200 ml.) gives pronounced relief; if repeated approximately weekly, the succeeding doses are even more effective. Eventually, the medication is needed less, and the pain is permanently relieved.

Psychosomatic orthopedic conditions in the aged are most difficult to manage. They are usually states of well-established conversion hysteria, manifested by pain, limp, and partial loss of function of almost any limb or joint. We usually advise some simple form of home treatment, such as is used for conditions that closely resemble these orthopedic ones (8). Warm baths, exercises and ethyl chloride sprays are adjunctive measures. Psychosomatic orthopedic conditions are rare in a happy institutional atmosphere, are uncommon in private office practice, but are extremely common in clinic practice.

TREATMENT OF FRACTURES IN THE AGED

Fractures in the aged are different from those in young adults or in children. The distribution of the affected bones is different; the surgical neck of humerus, femoral neck, distal end of radius, and the vertebral bodies are the bones most commonly involved in the aged. In the recuperative phase of therapy, purposeful activity will yield better results than vigorous calisthenic exercises (9). Aged osteoporotic bone in not adaptable to internal fixation with plates or screws, so these operations should be performed only rarely, and then only for very strong indications. Aged patients also tolerate prolonged bed rest poorly. The types of fracture in extremely osteoporotic bone tend to be different from those seen in normal bone. Transverse, non-displaced, partly impacted fractures of the shaft, and flake avulsion fractures are more common in osteoporotic bone.

Certain fractures are treated differently in aged patients. Fractures of the

surgical neck of humerus are immobilized with a plaster Velpeau bandage (a cloth Velpeau bandage will fall off and adhesive applied in large quantities to the skin is distressing) for about ten to fourteen days—until the acute, severe pain has subsided. Then, a sling is substituted, and gentle exercises are started, increasing in severity. Fractures of the *shaft of the humerus* cannot be treated in a hanging cast because it is difficult to prevent edema of the hand and dis-traction; we use a sugar-tong plaster splint closely applied to the arm, and also a sling, according to the method of Watson-Jones (10). *Avulsion flake fractures of the elbow* are common; application of an elastic bandage for a few days is the only treatment required.

Extremely common in the aged is the comminuted fracture of the distal end of the radius with impaction and volar angulation (*Colles' fracture*). The displacement is reduced under local anesthesia and a circular cast is applied with the hand in a position of ulnar deviation and slight carpal flexion. Immediate and continuous elevation of the hand for about a day and a half after manipulation is most important. Finger motion is carried out regularly. It is preferable to keep the cast on for seven or eight weeks rather than six weeks. Even with the longer period of immobilization, however, the position gained during the initial reduction is liable to be lost, with resulting malunion.

In a Colles' fracture with a severely displaced, severely osteoporotic distal radius, the initial correct anatomic reduction is rarely maintained throughout healing. Full carpal flexion and ulnar deviation (the Cotton-Loder position) may be successful anatomically, but the finger exercises are difficult to perform and the end-result is liable to be a stiff wrist or stiff fingers. This problem is so great that some centers have elected to perform resection of the distal end of the ulna shortly after injury. In a few cases in our series the results have been good, but no large series has yet been published. Irrespective of the method of fixation, it is important to ensure that the patient exercises the shoulder frequently, as there is a high incidence of stiff shoulder.

Fracture of the metacarpal neck (with dorsal angulation) is not rare in the aged. In younger patients, the Jahss technique (pressure reduction through the flexed finger) is used to push the fragment back into place, followed by immobilization in a position of full flexion. The technique of reduction works well, but if fixation for three weeks is maintained in a position of full flexion, severe stiffness of the proximal interphalangeal joint is the inevitable result, and some of this stiffness may be permanent. We use the Jahss reduction maneuver, but we immobilize the joint in less than full flexion. Some anatomic position is lost, but good function is achieved.

Compression fractures of vertebral bodies are so common as to be almost universal in very old persons. When caused by trauma and there are symptoms, the method of Nicoll (11) is recommended. We disregard the fracture, prescribe a corset for the relief of pain, and soon afterward start exercises to preserve muscle tone. The patient should not stay in bed for more than a week to ten days, but this is not always easy to accomplish, *e.g.*, it may be difficult to obtain a corset for a clinic patient. With the aid of the corset, the patient can become

ambulatory much sooner than if bed rest is prolonged until all symptoms subside (12). The differential diagnosis between traumatic compression fracture in an osteoporotic spine and a fracture in the presence of metastatic carcinoma is discussed in the earlier section of this paper.

Fractures of the pubic and ischial rami are fairly common in the aged. Even if bilateral, it is possible to apply a snug corset and start ambulation within a few days, because the fractures are not in the line of weight bearing. Ambulation is not easy, but it is far preferable to keeping the patient in bed.

Fractures of the femoral neck are the unsolved problem in orthopedics at the present time. *Intracapsular* (*transcervical*) fractures occur in an area with a poor blood supply and have a poor prognosis. The prognosis is dependent upon several factors, of which perhaps the most important is the direction of the fracture line (Pauwel's angle). If horizontal, the prognosis is good and this fracture will often heal without internal fixation; but we prefer to use a Smith-Peterson nail for fixation in order to permit ambulation and weight bearing, guarded by crutches, within a few days after the operation. If the fracture line is vertical, the prognosis is bad. The tendency in the past few years has been to use a femoral head prosthesis for this type of fracture; the results are good, in the absence of technical complications, but are almost never completely satisfactory. When the fracture line is midway between vertical and horizontal, there is a choice of treatment—nailing, osteotomy or prosthesis. The final answer has not yet been written to the problem of intracapsular fractures of the femoral neck.

Intertrochanteric fractures are also common—if anything, slightly more so than transcervical fractures. In our series, the average age of the patients with intertrochanteric fractures was somewhat higher than that of the patients with transcervical fractures. The prognosis for healing is better in the intertrochanteric type because the fracture is through highly vascular bone, but the prognosis for life is slightly worse. Many patients are not fit candidates for any operation. These we are forced to treat in traction (Russell technique). Both mortality and morbidity in this group are extremely high. However, with good nursing care and a co-operative patient, Russell traction can produce a better anatomic result than open reduction and, on the average, the mortality rates are about the same. Russell traction is also used for the occasional young patient with an intertrochanteric fracture, but for the great majority we use McLaughlin or Jewett fixation appliances (internal fixation). For patients who are too sick to stand any operative procedure, Russell traction or Buck's extension is used as a palliative measure.

Occasionally, aged patients are in such poor condition that any operation is out of the question, or at least unwise. Sometimes they have not walked for several years and have sustained a fracture by turning in bed. The use of internal fixation in these cases is not warranted; even if it were successful, it would not improve the patient. This type of patient, having been bedridden for several years, can easily tolerate several more weeks of bed rest.

Fractures of the greater trochanter are associated with a very high mortality. The reason may well be that the average age of the patients is higher than in

cases of transcervical or intertrochanteric fractures. We have records of 12 such patients, 6 of whom died in the hospital. When we decided to change the method of treatment from Russell traction to early ambulation with a corset, no such fracture cases were admitted for three years; recently, however, 3 were admitted. All were treated by early ambulation (wearing a corset) and the results were good; there was no permanent disability due to the fracture, although 2 of the fractures healed with medial displacement. One patient has bilateral nonunion of fractures of the greater trochanter but it causes minimal disability.

Fractures of the tibial condyle in the aged should be handled differently than in younger patients. If lateral instability of the knee is not severe, all that is necessary is an elastic bandage and early, protected ambulation and quadriceps exercises. If there is distinct lateral instability (frequent with depressed tibial plateau fractures), a cast is applied from above the ankle to below the knee, and another from above the knee to below the groin; they are joined with hinges (Forrester or bridge-table type). We insist on early motion, without weight bearing. Quadriceps exercises are also initiated. When quadriceps power approaches normal, the casts may be removed safely, to be replaced by elastic bandages. Then weight bearing can be started. Even with poor anatomic results, surprisingly good functional results (in the aged only) can be attained. Open reduction of a fracture of osteoporotic bone in this region is fraught with catastrophic difficulties.

Fractures of the *mid-shafts of the tibia and fibula* are common between the ages 55 and 75. Any treatment which involves nonweight-bearing ambulation is a problem. Ambulation on crutches, in a cast, is difficult enough, but when avoidance of weight bearing is added to the regimen, ambulation is often impossible for any patient with less than full physical vigor. We use the method of Wilson *et al.* (13). This involves putting Steinmann pins into the tibia at the tibial tubercle and into the os calcis; reduction on a special frame or on a fracture table; insistence on accurate reduction checked by x-ray examination; wedging if necessary; and encouragement of weight-bearing ambulation within a day or two of injury. Non-union is extremely rare and the rate of union is superior to that following internal fixation if accurate reduction is attained.

Non-displaced fractures of the lateral malleolus are fairly common in the aged, although much more common in younger patients. These fractures can be treated safely, at any age, with firm elastoplast strapping. Roentgenograms must be taken every week for the first three weeks to be sure that displacement of the ankle mortise does not occur.

The most difficult decisions concern those cases in which the fracture needs special, possibly open, reduction and the patient is of advanced years. The internist should be informed of the end-results following both simple and complicated forms of treatment. He should then try to estimate the number of years of life remaining for the patient as balanced against the possible dangers of anesthesia or open reduction. The decision should be made jointly with the surgeon. The most unhappy patients we have seen were those in whom a disabling injury occurring at age 70 remained uncorrected at age 80 or more.

SUMMARY

A review is presented of common painful orthopedic conditions in the aged, and their treatment. Particular attention is paid to the methods for treatment of fractures, emphasizing the difference between aged and young patients in this respect.

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MORTALITY AND MORBIDITY IN LONG-TERM INSTITUTIONAL CARE OF THE AGED

JOSEPH P. COSTELLO, JR., M.D.* AND GEORGE M. TANAKA, M.D.†

St. Louis Chronic Hospital, St. Louis, Missouri

INTRODUCTION

Long-term custodial care is usually permanent in deteriorating patients of advanced age; thus the time of entry into the institution usually provides important data that would otherwise be lost in the blurred process of dissolution that ends in the patient's death. Prevailing techniques for institutional admission deserve critical appraisal. At the present time the majority of long-term admissions to nursing homes are controlled by lay or para-medical persons, with only nominal consultation by the physician. The cumulative effect of the inherent errors in such non-medical decisions to confine aged persons permanently, should be carefully studied by the medical profession. Such errors result in great personal distress and a fantastic wastage of money and resources. The size of the problem is illustrated by the situation in the State of Missouri, where there were 17,142 nursing home beds in May 1960, compared to the hospital bed total of 32,390 in August 1958.

The following report presents a survey of all new patients admitted to St. Louis Chronic Hospital in 1958. This hospital in 1958 enjoyed the fortuitously unique position of being the prime source of referral for indigent, acutely disabled, older persons of the City of St. Louis. Community pressure for service allowed the medical staff full latitude in case decisions and in the establishment of proper definitive procedures for long-term admission, control and study.

ADMISSION PROCEDURE IN 1958

When a request for admission was received, an admission clerk mailed a complete application packet, containing forms for the physician's report and for routine factual admission data, together with an extensive background questionnaire covering past performance profiles. Upon return of this information, and full authorization, an Admission Service physician examined the applicant, the Social Service Department interviewed the applicant and the family, and the Finance Department studied the economic background. These details completed the Admission Board requirements.

A staff physician then ruled on the necessity and urgency of admission at the weekly Admission Board meeting. If the application was approved, a definite admission date was assigned. The major restrictive qualifications were that the applicants were residents of the City of St. Louis, did not have mental disease

* Medical Director, St. Louis Chronic Hospital; Instructor, Department of Internal Medicine, St. Louis University School of Medicine.

† Chief, Medical Department, St. Louis Chronic Hospital; Instructor, Department of Internal Medicine, St. Louis University School of Medicine.

or active tuberculosis, and were unable to afford private facilities. There was broad latitude in the diagnosis of mental illness, with emphasis upon trial admission, in accordance with our concept there is a basic difference between the geriatric patient with a mental disorder and the senile psychiatric patient.

Following admission, the patients were sent to an Admission Ward for a complete medical study designed to initiate a plan for total medical long-term care. The results of this study over an eighteen-month period are reported here.

ADMISSION APPRAISAL

This admission study is presented in terms of the systemic condition which was the prime cause requiring withdrawal of the patient from society. Tentative diagnoses were made on the basis of the reports of the private physician, the Admission Service and the Chronic Hospital Admission Ward physician. The general categories were in the following order of frequency: generalized arteriosclerosis, chronic brain syndrome, cerebral vascular accident, cancer, fracture (almost invariably hip fracture), diabetes mellitus, heart disease, neurologic disease, arthritis, deafness and blindness, arthritis, obesity, and amputation.

The difficulty in diagnostic assignments and the complexity of multiple diagnoses is fully recognized. These diagnoses were not made as much on the basis of pathologic changes as on the basis of the specific reason for the patient's withdrawal from society and subsequent admission to the institution. For example, the group with the primary diagnosis of "generalized arteriosclerosis" might include an elderly man with arteriosclerotic heart disease, Class I, chronic brain syndrome, arteriosclerosis obliterans and benign prostatic hypertrophy who, despite this multitude of individual pathologic diagnoses, required institutional care on the basis of generalized arteriosclerosis. Similarly, a patient with long-standing well controlled diabetes might have to be admitted because of "chronic brain syndrome." On the other hand, both of these cases might have had to be admitted because of a precipitating factor such as a fracture. If so, they would have been listed in the category of "hip fracture."

The diagnostic categories were but part of the Admission Ward evaluation. However, they are used in this report to indicate the admission, discharge and survival patterns (Table 1) of chronic illness in the 518 patients admitted in 1958.

AGE STATISTICS

The ages of the 518 patients at the time of admission were distributed as follows:

	Less than 50 yrs. old	50–59 yrs.	60–69 yrs.	70–79 yrs.	80–89 yrs.	90 yrs. old or more
Per cent[1] of males	2	2	6	15	37	1
Per cent of females	1	2	9	20	24	4

This is in accord with the general pattern of age statistics for both sexes.

Though the number of admissions was limited (518), we attempted a com-

[1] Percentage values reduced to whole numbers.

TABLE 1

TABLE 1

Mortality and Discharge Rates for 518 Patients in Whom the Inevitable Process of Dissolution Had Reached the Stage of Mandatory Institutional Care

Diagnosis	No. and % of Patients (Male/Female)	Mortality*			Discharge*		Institutional Survival* at 18 Mos. (M/F)
		1–6 Mos. (M/F)	7–12 Mos. (M/F)	13–18 Mos. (M/F)	1–6 Mos. (M/F)	7–18 Mos. (M/F)	
Generalized arteriosclerosis	127 or 25% (51/76)*	60 or 48% (30/30)	14 or 12% (5/9)	6 or 5% (1/5)	10 or 8% (3/7)	2 or 2% (1/1)	35 or 25% (11/24)
Chronic brain syndrome	118 or 23% (45/73)	19 or 16% (6/13)	5 or 4% (2/3)	9 or 8% (3/6)	9 or 8% (5/4)	5 or 4% (2/3)	71 or 60% (27/44)
Cerebral vascular accident	79 or 15% (39/40)	23 or 29% (11/12)	10 or 13% (6/4)	5 or 6% (4/1)	12 or 15% (4/8)	7 or 9% (4/3)	22 or 28% (10/12)
Cancer	43 or 8% (25/18)	32 or 74% (18/14)	4 or 9% (4/0)	1 or 2% (1/0)	2 or 5% (1/1)	—	4 or 10% (1/3)
Fracture	40 or 8% (13/27)	11 or 28% (3/8)	3 or 7% (1/2)	2 or 5% (0/2)	10 or 25% (6/4)	2 or 5% (0/2)	12 or 30% (3/9)
Diabetes	31 or 6% (5/26)	13 or 42% (3/10)	2 or 6½% (1/1)	2 or 6½% (0/2)	1 or 3% (0/1)	—	13 or 42% (1/12)
Heart disease	27 or 5% (7/20)	14 or 52% (3/11)	4 or 15% (1/3)	—	—	—	9 or 33% (3/6)
Neurologic disease	17 or 3% (7/10)	8 (3/5)	1 (0/1)	1 (1/0)	3 (1/2)	—	4 (2/2)
Arthritis	15 or 3% (4/11)	4 (3/1)	—	—	1 (0/1)	2 (0/2)	8 (1/7)
Deafness and blindness	10 or 2% (5/5)	5 (2/3)	1 (1/0)	1 (0/1)	—	1 (0/1)	2 (1/1)
Obesity	6 or 1% (0/6)	2 (0/2)	—	—	1 (0/1)	2 (0/2)	1 (0/1)
Amputation	5 or 1% (2/3)	1 (0/1)	1 (1/0)	—	1 (0/1)	—	2 (1/1)
Totals	518 or 100% (203/315)	192 or 38% (82/110)	45 or 9% (22/23)	27 or 5% (10/17)	50 or 9% (20/30)	21 or 4% (8/13)	183 or 35% (61/122)

* The percentages refer to individual diseases and were not calculated for smaller groups.

parison with statistics for the total community population. For this purpose, available 1950 census figures by age decades were compared with the data for the patients in the same age groups admitted to St. Louis Chronic Hospital. The percentages revealed that in 1958 the 60–69 year admission group constituted 0.1 per cent of the entire community population of that age; the 70–79 year admission group, 0.5 per cent of the correspondingly aged population; the 80–89 year admission group, 1.9 per cent; and the 90-plus admission group, 3.4 per cent.

MORTALITY RATE

The data on mortality and discharge rates are shown in Table 1. Mortality was high (38 per cent) in the first six months, but during the second six months it had dropped to 9 per cent, and in the third six months to 5 per cent.

The discharge rate was 9 per cent in the first six months, and 4 per cent in the subsequent year.

At the end of the 18-month period of study, the survival rate was 35 per cent.

DISCUSSION

These figures on admission prognosis should be viewed in the light of the relationship of St. Louis Chronic Hospital to other facilities for the care of the aged during the year 1958. In the metropolitan area of St. Louis, most of the geriatric services concentrate upon the older person in the initial stages of his life in an institution. This stage might be considered as the domiciliary home, or supervised boarding home. It represents the major community effort, partly because of the large volume of patients and partly because of the technical problems of providing more advanced nursing care. Many of the 518 patients admitted to the St. Louis Chronic Hospital came from such a sheltered environment, and consequently they required more than simple supervision with room and board. These patients had passed the point where mere supervision would suffice. Active participation by the institution was necessary in the nursing and rehabilitation field.

When illness in the later years is serious enough to disrupt the living pattern and result in long-term institutional care, the prognosis is grave. Perhaps the most significant finding was the high mortality rate in the first six months. This high immediate mortality was of great concern to the medical staff of the hospital. In an effort to determine the cause, all applications were checked from January through June, 1959. Among a total of 454 applicants accepted by the Admission Board, 47 or 11 per cent had died before their admission date. The time-interval did not exceed one month. This further emphasizes the serious prognosis in such cases.

The decrease in mortality for patients capable of surviving more than six months is noteworthy since it indicates that, irrespective of the mental or physical defect, a patient capable of adapting to the environment can maintain life in the most advanced stages of physical and mental deterioration.

The discharge rates indicate that an aggressive program to rehabilitate

patients can be successful in a substantial percentage of apparently hopeless cases.

The direct application of these findings to the problem of chronic illness lies in the fact that the very persons who can be returned to the community are those most likely to survive for many years in hospitals for the treatment of chronic disease.

SUMMARY

Appraisal of the 518 admissions to St. Louis Chronic Hospital during the year 1958 is presented in terms of age groups and medical disability as applied to the mortality rate, discharge potential and survival pattern. The high mortality during the first year of institutional care in a chronic disease hospital is stressed. It is correlated with the stepwise pattern of deterioration according to aging.

Decisions regarding long-term institutional admission should be made only on the direct recommendation of the physician, after adequate planning and therapeutic trial disclose the inability of the patient to continue community existence.

PSYCHOLOGY OF BEHAVIOR IN THE CLOSING YEARS

RICHARD ASPINALL, PH.D.*

Fort Lauderdale, Florida

A practical definition of psychology is the study of behavior. The "closing years," as discussed in this article, arbitrarily refer to the remaining years of retired people in fairly good health, beyond the age of 70. In early life, as well as throughout adolescence and middle age, people generally give little heed to the end of life; but when they arrive at the age of senescence they think more of death's connotations than of anything else. It may be assumed that no specific age group appreciably understands any other age group. For example, the youngsters are not able to appreciate the viewpoints of the matured, because they themselves are not mature; and, by the same token, the middle-aged do not understand the reasonings of retired persons.

Grim reminders of death come to virtually everyone sooner or later, by one incident or another. The writer recalls one such incident the day after war was declared by the British against the Germans in the autumn of 1939. We were busily engaged in preliminaries for embarkation to the United States from Southampton, England. At the same time and at the same port, thousands of other American tourists with later reservations were making frantic efforts to board our ship, which was the first outgoing United States liner since hostilities had begun. Our original passenger list was more than doubled, but a vast crowd of anxious American citizens had to be left at the dock.

It was evening as we set sail with our ship's lights in full glare; and thus they remained throughout each night of the entire trip, since our country was not yet at war. (Incidentally, we saw two British owned and operated passenger liners leave for the United States completely blacked out.) Our bedroom stewards told their respective quotas of passengers each night just where their particular life boats and life belts were located. My boat was #26, and my belt was #17, and I needed no promptings to remember those numbers. My great concern was whether the German submarines had my numbers. Many passengers never went to bed, or even dressed for bed, during the entire voyage. Everybody was pensive, and not very conversational. There were no public meetings, other than the different church services on the Sabbath Day. A few encouraging messages came over the loud-speaker system from the Captain of the ship, and a message of assurance from President Roosevelt, relayed to us by Postmaster General Farley, who was a fellow passenger. When we got out of sight of land, some lyrics of a Sunday School hymn came to mind over and over again:

> I know not what awaits me,
> God kindly veils my eyes,
> And o'er each step of my onward way
> He makes new scenes to rise.

* *Address:* 1534 N. E. 16th Terrace, Fort Lauderdale, Fla.

> And every joy He sends me comes
> A sweet and glad surprise.
>
> So on I go not knowing,
> I would not, if I might,
> I'd rather walk in the dark with God
> Than go alone in the light.
> I'd rather walk by faith with Him,
> Than go alone by sight.

These lines may not reflect highly accepted theology, but they were a benediction in a situation where everyone was apprehensive of the nearness of death, yet none seemed to be discussing it at any time or in any place. At long last, we sighted the homeland, and began to act as though nothing out of the way had happened. It may be better thus.

This discussion seeks only to break down into general patterns the behavior of the writer, or the reader, or any other given person in his vintage years, assuming that he enjoys a fair measure of health during that period.

It does not come within the province of this article to discuss the merits or shortcomings of eschatology, regardless of their importance. All-important, however, is what any given person thinks as he nears the last portals, if and when it reflects his attitudes toward himself and the world at large. The journey along the "last mile" may be a bold venture, or a blissful waiting or perchance an inescapable tragedy, but it is a path that must be traveled alone. Think how many are giving up their entire life's savings as a mortgage in order to pay for hospitalization and medication, so they may remain here for a few months or even weeks. Such procedures haunt elderly people as a "stay of execution." On the other hand, the more sensible attitude for the oldster to adopt is to evaluate his own milieu continuously and strive to make his last days his happiest ones. This is no easy assignment. Yet it is axiomatic in the years of active work that folks do themselves the greatest service when they meet situations as they arise. It would be folly to change that policy at retirement age. There have been millions of printed words, and there will be millions more, that advocate what oldsters as a class should do or not do, but the present primary need is a definitely outlined policy for the individual. Each of us must come to grips with his own situation.

The answer to real progress is appropriate research, and for those in retirement the answer is for more and more research in geriatrics made by members of their own group. One objective of these studies should be information that will aid us to meet the shrinking-dollar problem. The bitter truth obtains that all who saved up enough for comfortable retirement now find these assets have less than half of the purchasing power of a few years ago, in all markets; and the end of this frightening depreciation process is not nearly in sight.

SELF-ENLIGHTENMENT

Happily, there is a brighter side to this picture. Self-enlightenment will pay incomparable dividends in at least three areas:

1. The elderly person should be aware of the fact that the moment he was

born, he began to die. Those who are not yet born may emerge from the stream of life in later generations, and those who never become parents have no biologic part in the life stream, except to be born in it. The "Riddle of the Universe" affects us all. We look wistfully to any source that may assist us in our thinking, but real help is not easily available. The existentialists, who are getting a big play these days, blur the issue by insisting that existence precedes essence, and that man is simply what he carves out for himself by virtue of his status in existence. Anyone may argue pro and con or postulate about pre-existence or immortality, without adding to or detracting from the Great Riddle, so long as his chanting remains within the realm of metaphysics. The geneticists, who make much of the chemical formulae in their relations to the thread of life, do not add to our knowledge in terms of where we first came from, or whither we are ultimately bound. The individual becomes aware of himself when he finds he is part of creation, and he learns that for himself, if he ever learns it. Since no one knows who he himself is or ever was, until he becomes 3 or 4 years old in this specific life, and no one knows who he himself will be in the hereafter, why should he give much heed to scientists of any name who have no basis in fact for their conclusions? It is the height of folly to cast aside a sustaining faith in a benevolent Creator in exchange for a theory, no matter who formulated it.

2. The retired person should cultivate an awareness of the state of his metabolism. It would be good practice for retired people to greet each other with the query: "How's your metabolism today"? In lay terms, metabolism may be regarded as the building up and breaking down of energy stores within the body. When the patient is sluggish, his metabolism is low; when he is energetic, his metabolism is high. Metabolism is regulated by the endocrine glands which release their secretions into the bloodstream as hormones. There is a positive tendency in the body at all times towards a balanced internal status. This is professionally known as homeostasis. The final balance, or imbalance, is the indicator of our physical and mental condition. We build up to our best physical balance in about our twenty-third year; after that age we deteriorate in varying degree, until the end of life's span. It is a full-time assignment as we grow older, to watch over our blood pressure, heart condition, and guard against the possible mental and bodily ailments to which man falls heir. The body wears out somewhat like an automobile but, sad to relate, very few new parts are available. Conservation of mind and body demands a rigid schedule of conduct, as well as perhaps scads of pills and many medical and psychologic aids.

3. The normal person is already aware that he cannot prolong indefinitely his length of days, but he may live more contentedly and consequently somewhat longer by serious application of psychosomaticism. This high-sounding term means no more than the power of the mind over the body, but it is silly to apply frivolous connotations to such a well established principle. There are both harmful and helpful aspects of this rule of action. The former is reflected in the patient with virtually no physical signs who broods over a supposed ailment so much that he works himself into a most pitiable condition. Then there is the oft-repeated story of the power of suggestion, in which 4 or 5 acquaintances

casually remark to a fellow man during the course of a day, how ill he looks, so that the poor man is in a hospital within a week though there was nothing physically wrong with him. The helpful aspects are exemplified when sensible people apply curbs on the quantity and quality of the food they eat; on what, and how much, they drink; and when they practice moderation in some, and total abstinence in other indulgences. Psychosomatic diseases are physical ailments caused by psychologic stress. For this reason, hypnosis may play a role in treatment.

Most people want to live as long as possible here, and then live in the hereafter, meanwhile hating death because it is the enemy of life and the common enemy of man. Thus life assumes greater and greater significance to the elderly who, by definition, are near death's portals. Another birthday is a crisis; to live another month in fairly good health is a real cause for thanksgiving. Faith in God comes only to those who seek it. There is no point in trying to save face when in contact with those who repudiate future life, just because they seem perplexed and are probably annoyed by reason of the perplexity.

William James, an all-time "great" in psychology, in his *Will to Believe* used the following quotation from Fitz-James Stephen's *Liberty, Equality, Fraternity:* "If a man chooses to turn his back altogether on God and the future, no one can prevent him; no one can show beyond reasonable doubt that he is mistaken. Each must act as he thinks best; and if he is wrong, so much the worse for him. What must we do? 'Be strong and of good courage.' Act for the best, and take what comes. . . . If death ends all, we cannot meet death better."

HYPERTENSION AND EDEMA IN THE AGED: OBSERVATIONS ON THE USE OF A MEPROBAMATE-HYDROCHLOROTHIAZIDE COMBINATION

WESLEY W. BARE, M.D. AND HARRY L. BAIRD, M.D.

The Methodist Home for the Aged, Philadelphia, Pennsylvania

In a previous study at the Methodist Home for the Aged we demonstrated the antihypertensive activity of hydrochlorothiazide in elderly patients (1). The drug was found to be effective in smaller dosages when combined with a synthetic reserpine derivative. Since many geriatric patients display emotional upsets for relatively minor reasons (2), addition of a tranquilizer should alleviate much of the tension associated with hypertensive disease, and perhaps allow for a minimal dose of diuretic substance.

We therefore became interested in a new combination tablet[1] consisting of 200.0 mg. of meprobamate and 25.0 mg. of hydrochlorothiazide, and evaluated its use in a similar group of hypertensive or edematous patients.

METHODS AND MATERIALS

The study was carried out over a three-month period, on 45 geriatric patients at the Methodist Home for the Aged in Philadelphia. Their ages ranged from 71 to 87 years. All partook of a standard diet, but were instructed to refrain from using salt at the table for seasoning. No other effort was made to prepare special salt-free diets, but each patient was instructed to drink at least one glass of citrus juice daily to assure adequate potassium intake. A level of 150/100 mm. Hg was taken as the normal blood pressure (1, 2) and an increase in either systolic or diastolic pressure was considered to be hypertension. Only patients who presented themselves at sick call with symptoms suggestive of hypertension or edema were selected. Patients with normal blood pressure were also studied but these had edema severe enough to warrant regular use of a diuretic, and only those who needed a tranquilizer were selected. Patients who were already taking diuretics or antihypertensive medication were given a placebo for two weeks before beginning the new drug.

Before starting therapy, blood was drawn for determination of blood urea nitrogen (BUN), sodium and potassium levels. Treatment of all patients was then started with the combination tablet. The dosage was one tablet three times a day, and after approximately four to six weeks it was reduced to two tablets a day. This was in keeping with the results of our previous study in which we found that smaller maintenance doses had as good a clinical effect as did larger doses, yet caused fewer electrolyte disturbances. After four more weeks the BUN and electrolytes levels were again determined. Dosage was then gradually reduced on an individual basis until a maintenance dose satisfactory for control of the edema or hypertension was found. A final series of laboratory studies was performed after completion of the investigation three months later.

Patients already taking additional drugs such as digitalis or coronary dilators were permitted to continue them. All patients were seen at least once a week and at each visit records were kept regarding weight, blood pressure, edema, and the presence or absence of such symptoms as dyspnea, dizziness or headache. The laboratory findings were recorded. All clinical evaluations were made by one person (WWB).

[1] Miluretic (Wallace Laboratories).

RESULTS

Changes in blood pressure, the amount of edema, body weight and blood chemical levels are objective factors which lend themselves to accurate determination. The patient's symptoms are equally important, but are subjective in nature and not as reliable.

Blood pressure

The blood pressure was determined at each visit. For comparison, the average systolic, diastolic and pulse pressures were calculated at the time of the initial visit, at a point mid-way in the study, and at the conclusion of the study. Figure 1 shows the data. At the first visit the average systolic pressure was 178 mm.

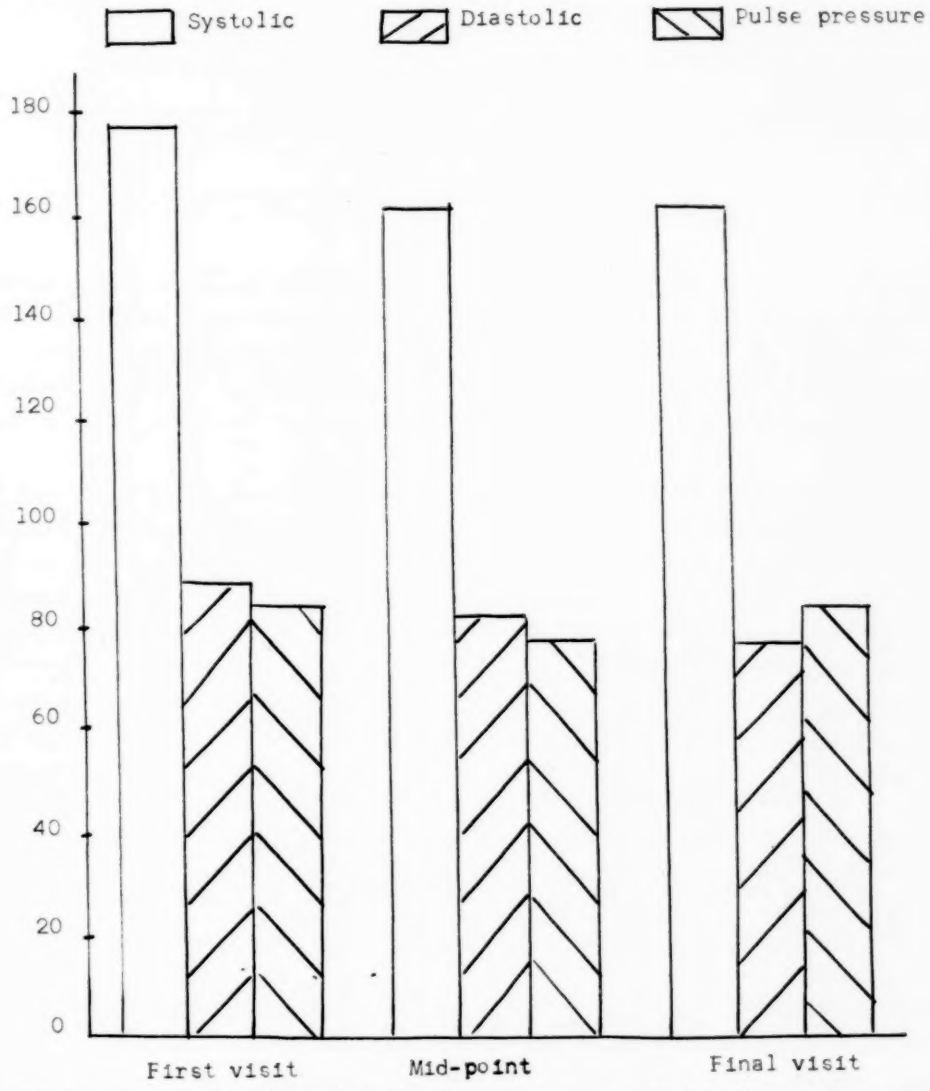

FIG. 1. Average systolic, diastolic and pulse pressure (mm. Hg) in 54 geriatric patients.

Hg. By the final visit, it had subsided to 161 mm.—a decrease of 9.8 per cent. The average diastolic pressure was 88 mm. at the beginning and dropped to 78 mm. by the third visit—a reduction of 1.4 per cent. It is interesting that the pulse pressure remained relatively constant at 84 mm. Hg.

Since in many of these patients there was no real hypertension to start with, and edema may have been the only symptom requiring treatment, the entire group was divided in half on the basis of the blood pressure (B. P.) readings. When this was done the readings in the high B. P. group were decreased by the drug much more than the readings in the lower B. P. group (Tables 1 and 2). The drug was therefore more efficient as an antihypertensive agent in the group with the higher blood pressure.

Mean arterial pressure

The mean arterial pressure (MAP) was calculated by two methods:

$$MAP_1 = \text{diastolic pressure} + \frac{\text{pulse pressure}}{3}.$$

$$MAP_2 = \frac{\text{systolic pressure} + \text{diastolic pressure}}{2}.$$

Figures 2 and 3 show the data with each of these methods. There was a significant reduction in the MAP between the first and the final visit, by both methods of calculation. The average MAP_1 dropped from 134 mm. Hg to 119 mm.—a reduction of 11.2 per cent. The reduction in the higher B. P. group of patients was greater, with both methods of calculation, than in the lower B. P. group.

TABLE 1

Changes in Systolic, Diastolic and Pulse Pressure in the 50 Per Cent of Patients with the Highest Blood Pressures

	Pressure (mm. Hg)		Decrease (%)	Pressure (mm. Hg), Final Visit	Decrease (%)
	First visit	Second visit			
Systolic pressure	200	167	16.5	170	15.0
Diastolic pressure	95	87	16.3	79	16.8
Pulse pressure	101	114	—	91	—

TABLE 2

Changes in Systolic, Diastolic and Pulse Pressure in the 50 Per Cent of Patients with the Lowest Blood Pressures

	Pressure (mm. Hg)		Decrease (%)	Pressure (mm. Hg), Final Visit	Decrease (%)
	First visit	Mid-point			
Systolic pressure	160	156	2.5	153	4.6
Diastolic pressure	82	79	3.7	71	13.4
Pulse pressure	68	76	—	71	—

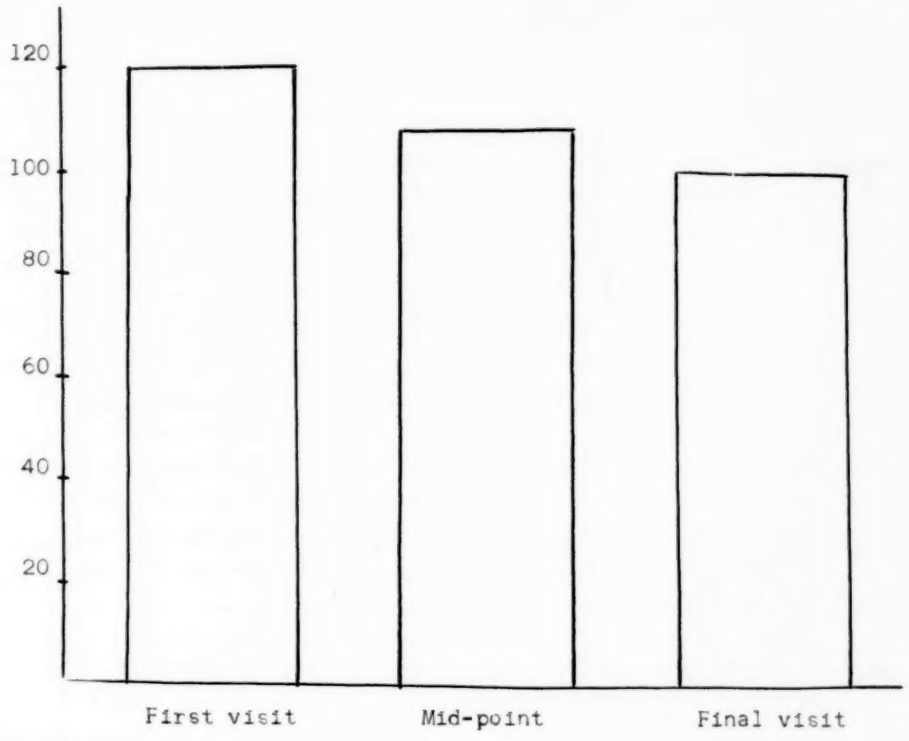

FIG. 2. Average mean arterial pressure[1].

$$MAP_1 = \text{diastolic pressure} + \frac{\text{pulse pressure}}{3}$$

When the blood pressure records were divided into 5 equal groups from the highest to lowest, the MAP showed a much greater change in the higher B. P. group. Three fiducial limits (99.7 per cent) were calculated for each MAP. There was significant reduction in both groups of patients. The upper limit was reduced from 199.1 mm. Hg to 145.6 mm. This indicates that in a similar group of patients an average reduction could be expected in 99.7 per cent of the cases in which the drug was used. The large reduction in the upper limit is due to a lowering of the average and a decrease in dispersion between the first and final visits.

Edema

The clinical measurement of edema is not exact. In order to minimize error, all evaluations were made by one person and the gradation recorded in the classic 1-plus to 4-plus manner (1). This classification is admittedly ill-defined and has certain drawbacks, but it is the one commonly used in the everyday practice of medicine.

Figure 4 shows the results. The findings were tabulated for the beginning, mid-point and end of the study. At the beginning, 45.5 per cent of the total group of patients had clinically detectable edema of varying degree; at the mid-point this proportion was reduced to 13.0 per cent; and at the end of the study, only 5.0 per cent of the patients had edema. Four patients had temporary increases in edema and required an increase in dosage, but only for a few days.

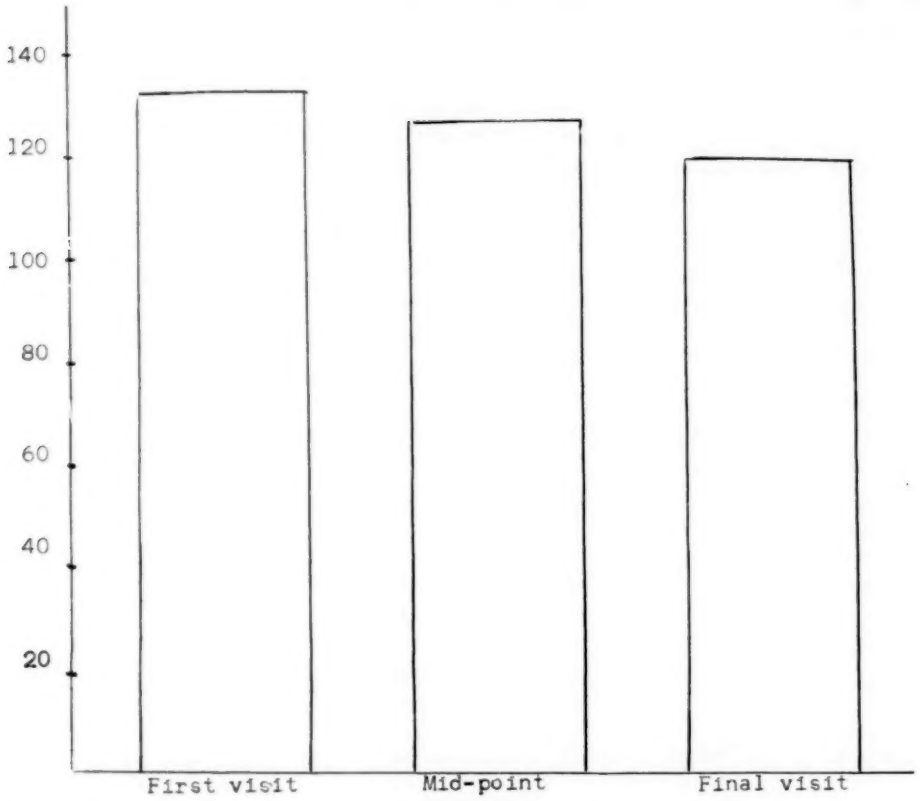

FIG. 3. Average mean arterial pressure[2]. $MAP_2 = \frac{\text{systolic pressure} + \text{diastolic pressure}}{2}$

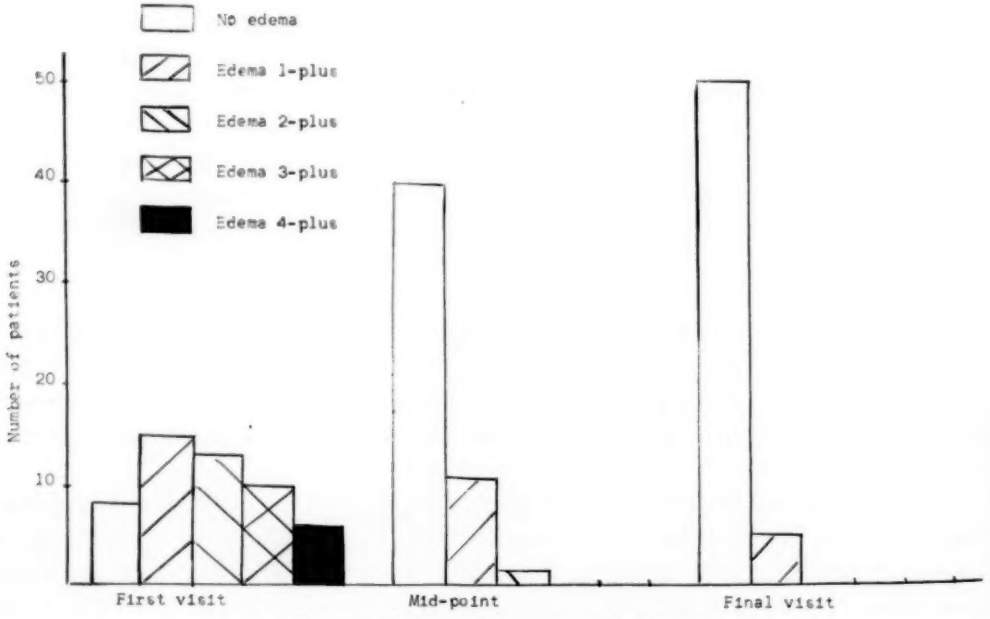

FIG. 4. Changes in amount of edema.

In no case was it necessary to resort to injectable mercurials, although several patients had been previously receiving them.

Body weight

Table 3 shows the changes in body weight during the study. Weight is intimately connected with the amount of fluid retained in the body, and decreases in proportion to the increase in excretion of fluid. For the entire period, the average weight loss was 4 pounds.

Levels of blood urea nitrogen, and serum sodium and potassium

Table 4 shows the blood chemical data. (Normal *blood urea nitrogen* (BUN) levels in this laboratory range from 7.0 to 17.0 mg. per 100 ml. of whole blood.) In no patient was there an elevation above the upper limit of normal. It may therefore be assumed that all had reasonably adequate renal function. Throughout the study the concentration of BUN remained remarkably constant.

The serum *sodium* level also remained constant. (Normal values in this laboratory range from 134 to 140 mEq. per liter.) This is in keeping with our previous experience, but is at variance with reports (3) indicating that hydrochlorothiazide increases sodium diuresis.

The major problem with diuretic drugs is the loss of *potassium* by way of the urine. (Normal values for serum potassium concentration range from 4.1 to 5.7 mEq. per liter.) In this study there was a *rise* in the serum potassium level from 3.9 mEq. to a final 5.1 mEq. per liter. Meprobamate does not contain the potassium ion, and hydrochlorothiazide depresses the serum potassium level (1). Therefore the rise in serum potassium concentration in our series would seem to be attributable to the liberal amounts of citrus juices ingested by each patient

TABLE 3

Changes in Body Weight

	Body Weight (lbs.)		
	Average	Range	Average loss
First visit	137.5	105–228	—
Mid-point	135.0	105–224	2.5
Final visit	133.5	104.5–222	4.0

TABLE 4

Changes in Blood Chemical Levels

	BUN (mg./100 ml.)	Sodium (mEq./L)	Potassium (mEq./L)
First visit	12.5	137	3.9
Mid-point	12.4	137	4.0
Final visit	12.5	136	5.1

daily. This ready source of potassium was apparently enough not only to prevent hypokalemia, but to correct any pre-existing deficiency.

Side-effects

Two patients (3.8 per cent) displayed symptoms such as lethargy or drowsiness which could have been caused by meprobamate. Both of these patients were somewhat senile. After discontinuation of the drug there was moderate, but not complete, improvement. In no patient in the series were there any clinical manifestations which would suggest hypokalemia.

COMMENT

This combination of meprobamate and hydrochlorothiazide exerts an antihypertensive effect equal to that of hydrochlorothiazide alone. The meprobamate undoubtedly aids in controlling the anxiety and agitation so frequently seen in the geriatric patient. The higher the initial blood pressure, the greater will be the response to the drug. Since hypotension develops in patients whose initial blood pressure is in the lower ranges, this drug combination is useful in the control of edema in the normotensive subject.

The addition of potassium supplements to the diet is advisable. In this series, ingestion of citrus juices daily was enough to prevent disruption of potassium balance, so that administration of potassium chloride was unnecessary. Restriction of sodium need not be severe, since prolonged diuretic therapy allows for relaxation in this regard. Our patients were instructed to refrain from the use of salt at the table, but were otherwise given the same diet served to all others in the institution. Serum sodium levels remained constant.

SUMMARY AND CONCLUSIONS

The effect of oral administration of meprobamate (200 mg.) and hydrochlorothiazide (25 mg.) combined in tablet form was evaluated in 54 geriatric patients in a home for the aged. All had hypertension or edema, or both, and were treated over a period of three months.

A definite decrease in systolic, diastolic and pulse pressures was observed during treatment. The decrease was more pronounced in the patients with the higher initial blood pressure readings. Adequate diuresis was obtained in the edematous patients. Serial determinations of the blood urea nitrogen and serum sodium levels showed no significant change. There was no evidence of hypokalemia; in fact, the serum potassium level rose slightly (probably in association with the daily ingestion of citrus juices).

Side-effects were minimal (lethargy and drowsiness) and were noted in only 2 patients.

This combination of meprobamate and hydrochlorothiazide in dosages of two or three tablets daily is an efficient and safe antihypertensive and diuretic agent. It is therefore valuable in the management of geriatric patients with hypertension or edema.

Acknowledgment

We are grateful to Wallace Laboratories, Cranbury, New Jersey, for the generous supplies of "Miluretic" used in this study.

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THE CONTROL OF GASTRO-INTESTINAL HEMORRHAGE IN CIRRHOSIS BY COMBINED ADRENOCORTICAL AND ESTROGENIC THERAPY

H. J. ROBERTS*

West Palm Beach, Florida

The proposal of a pharmacologic regimen for the management of massive gastro-intestinal bleeding in cirrhosis of the liver at once engenders a certain amount of skepticism among medical experts in this field, particularly when the proposal is based upon observations in a limited number of patients and when one of the agents is potentially ulcerogenic. On the other hand, the striking beneficial and even life-saving effects observed following the combined use of estrogens intravenously and adrenocortical steroids parenterally in 5 severe cases of Laennec's cirrhosis and primary biliary cirrhosis justify the recording of these experiences. Most of these patients were seen in consultation after treatment with massive quantities of blood, vitamin C, vitamin K, topical thrombin, calcium and a host of other drugs and procedures had proved ineffective.

Discussion of the subject with a number of gastro-enterologists and internists interested in the management of gastro-intestinal hemorrhage failed to uncover another clinic in which this particular pharmacologic approach is employed. One hematologist recalled using estrogens intravenously for the management of gastro-intestinal hemorrhage in portal hypertension, with striking benefit. A search of the literature produced but one report in which severe hematemesis in a patient with portal cirrhosis and esophageal varices (proved at autopsy) rapidly and repeatedly responded to intravenous estrogen therapy (1).

Although our data are too limited to permit statistical analysis, they would seem to be worth reporting, because of the importance of *any* new form of treatment that can control variceal bleeding associated with cirrhosis of the liver and can tide patients over this critical period. This is emphasized by the following facts: 1) this disease is now one of the 10 leading causes of death in the United States, being exceeded in the 45–64 year age group only by heart disease, cancer, and cerebral hemorrhage; 2) severe and exsanguinating hemorrhage from rupture of the associated esophageal varices is one of the major causes of the fatalities (at least half the patients do not survive two months); 3) the alarmingly high *early* mortality rate has not been lessened by surgery; 4) there is an acceptable survival rate despite the initial heavy death toll from hemorrhage; and 5) the gastro-intestinal bleeding frequently recurs after treatment by portacaval or splenorenal shunt. The virtually unchanged prognosis following venous-shunt operations in patients who have bled from these varices, the operative mortality of 20 per cent even in experienced hands, and the fact that selected cases often do as well with purely medical therapy, has disenchanted a number of gastro-enterologists with the results of such surgery (2). In a recent authoritative review

* *Address:* 1525 North Flagler Drive, West Palm Beach, Fla.

of the treatment of bleeding esophageal varices, Leevy, Cherrick and Davidson (3) state: "It is quite clear that variceal hemorrhage in many patients with cirrhosis cannot be treated by shunt surgery, for they are unable to tolerate the operation. Indeed, in a large segment of patients with cirrhosis, the bleeding episode is only one of several clinical abnormalities incident to liver failure and a fatal termination." The magnitude of the mortality in cases of cirrhosis with hemorrhage from varices continues to be so high that prophylaxis by means of shunt surgery is advocated in some centers (4).

The problem assumes even greater proportions when considered in the light of the clinician's frequent inability to ascertain the mechanism and site of the massive hemorrhage, and the dynamic capacity for constant change in esophageal varices. Even with the use of esophagoscopy and special roentgenologic technics (including splenoportography), esophageal varices are demonstrable in less than one-fourth of these patients (3). Furthermore, in some instances neither intrahepatic nor extrahepatic portal-vein obstruction can be demonstrated as the cause of portal hypertension and massive bleeding from esophageal varices (5a); the cause may be increased blood flow through the portal vein. Even in cirrhotic patients who are candidates for portacaval or splenorenal shunt, the possibility of a spontaneous decrease in portal pressure with accompanying clinical improvement exists. This occurred in half of a group of patients with "decompensated" alcoholic cirrhosis who received prolonged hospital care (5b).

Several additional aspects of such hemorrhage serve to emphasize certain shortcomings in our present approach to the problem. Balloon tamponade with the Sengstaken tube or the Linton tube unquestionably has been life-saving in many instances of persistent variceal bleeding, yet the introduction of this procedure has had little influence on the mortality rate for the majority of poor-risk patients with bleeding esophageal varices and liver failure who are seen in large municipal hospitals (3). The gastric balloon has to be properly and skillfully fitted in order to restrict entry of blood into the esophagus, and certain complications are inherent in such tamponade, *viz*, tearing, ulceration or rupture of the esophagus, reflux of blood from the esophagus of obtunded patients, obstruction of the airway caused by displacement of the balloon, and cardiac arrhythmias associated with distention of the esophagus. There may be concomitant multiple ulcerations in both the stomach and duodenum in cases of esophageal bleeding. The administration of vitamin C, vitamin K or vitamin K_1 preparations is usually futile; in fact, large amounts of vitamin K parenterally can further insult the liver (6). These limitations are understandable in the light of the frequency with which various clotting abnormalities occur in cirrhosis. For example, one report cites the following incidence of clotting deficiencies in a group of cirrhotic patients: 50 of 58 were deficient in prothrombin, 31 of 36 were deficient in Factor V, and 30 of 36 were deficient in Factor VII (7). A functional platelet defect—demonstrable by means of the thromboplastin-generation test, and designated as thrombasthenia—also has been demonstrated in two-thirds of patients having severe liver disease, with or without concomitant numerical

platelet deficiency (8). There is further evidence to suggest that platelet function may be decreased after acute gastro-intestinal hemorrhage (8).

CLINICAL STUDY

Five cases of severe hepatic cirrhosis were studied. The estrogenic preparation employed was Premarin Intravenous.[1] The drug usually was administered in a dose of 20 mg., as a slow intravenous infusion. This substance is supplied in the form of individual "Secules," each containing 20 mg. of estrogen in a naturally occurring, water-soluble conjugated form, expressed as sodium estrone sulfate. The material was slowly reconstituted immediately prior to use by adding the contents of the accompanying 5-ml. vial of sterile diluent containing 0.5 per cent phenol, U.S.P. If not exposed to light, the resulting clear solution can remain stable at room temperature for periods of from sixty to ninety days. Slow injection obviates the occurrence of flushes. In seriously-ill bleeding patients, the drug was injected into the tubing through which blood, dextrose, or fructose solutions were being administered. (Premarin Intravenous is not compatible with protein hydrolysates, ascorbic acid, or solutions having an acid pH.) When the gastro-intestinal hemorrhage was massive, the estrogen was injected as often as every six to twelve hours, and then continued at daily intervals until it was clinically apparent that the hemorrhage had stopped.

The intramuscular route of administration was avoided. Others have observed that there is a prompt fall in the excretion of sodium and chloride, along with retention of water, for a period of several days when estradiol is administered intramuscularly (9). This does *not* occur when the intravenous route is employed; furthermore, with such short-term therapy, hyperestrogenic effects are not produced. On repeated occasions, the author has observed that some patients with diabetic glomerulosclerosis, previous or existing heart failure, and chronic liver disease experience fluid retention when given estrogens orally, whereas no retention occurs when the estrogens are given intravenously. The absence of such effects when the intravenous route is employed can be explained by: 1) rapid excretion of the hormone from the body so that there is little opportunity for it to act on either the kidneys or the target organs, and 2) rapid metabolism of the estrogen and its conversion into other nonactive metabolites. The author has treated more than 80 cardiac patients with estrogens intravenously, either for the control of associated severe symptomatic prostatism, stress incontinence, or the management of acute bleeding episodes during long-term anticoagulant therapy, but has not observed any significant degree of salt or water retention (10). In the present series also, the fear that combined estrogen-adrenocortical steroid therapy would result in sodium, chloride and water retention proved groundless.

Estrogens can produce anemia and aplasia of the marrow experimentally (11, 12), but this has not proved to be a deterrent in patients receiving large doses of estrogens intravenously and moderate doses by mouth. Thrombocyto-

[1] Kindly supplied by Ayerst Laboratories, New York City.

penia associated with estrogen therapy has been observed by others only on rare occasions (13).

The adrenocortical steroid preparation employed in most of these studies was cortisone acetate, given intramuscularly. During the initial critical phases, the dosage was 75–100 mg. every six to eight hours, care being taken that the drug was injected into the deltoid muscle area (to obviate difficulties in absorption). More recently, dexamethasone (4–8 mg. intramuscularly or intravenously every six to eight hours) was used. Once bleeding began to subside, the dose was gradually reduced, followed in turn by a shift to an adrenocortical steroid preparation that could be given orally. Steroid therapy usually was discontinued within a week following cessation of active bleeding.

Although blood in the stomach acts as an effective antacid substance, supplementary antacid preparations were administered orally once the bleeding had terminated, in order to obviate any tendency toward the development of a steroid-induced ulcer. This was particularly pertinent in the presence of associated alcoholic gastritis.

RESULTS

Control of persisting gastro-intestinal hemorrhage was achieved in the 5 cirrhotic patients (in one of whom the disease was primary biliary cirrhosis). This response usually was apparent within twelve to sixteen hours after the institution of therapy. On 3 occasions, many transfusions of fresh blood had not controlled the bleeding at the time treatment with combined steroids was instituted. In none of the patients was a concomitant gastric or duodenal ulcer demonstrated by x-ray examination following control of the bleeding.

The case histories of 2 cirrhotic patients with hemorrhage who demonstrated an apparent clearcut clinical response are presented. Also included is the case history of an alcoholic patient with a large liver and massive gastro-intestinal hemorrhage who responded promptly to combined hormonal therapy, but in whom subsequent studies revealed only an active duodenal ulcer. [This effect also has been observed in several cases of bleeding peptic ulcer following the administration of intravenous estrogens (14).]

CASE REPORTS

Case #1

W. K., a 43-year-old roofer, was first seen in consultation at the request of his attending surgeon. The patient had been admitted with massive hematemesis and tarry melena three days previously. The hemorrhage had persisted along with increasing coma, notwithstanding numerous transfusions, vitamin K_1 oxide, vitamin C, and a correctly inserted Sengstaken tube. Death seemed imminent. The patient was a chronic alcoholic and had experienced a hemorrhage from his gastro-intestinal tract approximately nine months previously. He had been subjected to a splenectomy, but a portacaval shunt procedure was not deemed feasible at that time. He had been getting along fairly well until one week prior to the present admission, when tarry stools were noted after his resumption of excessive drinking.

Physical examination revealed an obese white male in profound coma, not responding even to maximal stimuli. His pulse was 120 and regular, blood pressure 170/80 mm. Hg, and

temperature 103.2°F. (rectally). There was considerable frothing at the mouth, as well as stertorous breathing. Coarse, moist rales could be heard in the lungs bilaterally. The liver was palpable three fingerbreadths below the right costal margin and in the epigastrium, and there was slight ileus. Babinski responses were present bilaterally. Profuse quantities of tarry liquid stools were being passed.

The author's initial impression was hemorrhage from both esophageal and gastric varices secondary to the cirrhosis and portal hypertension. Additional possibilities included a bleeding peptic ulcer, hemorrhagic gastritis, or a hemorrhagic diathesis secondary both to liver disease and to excessive citrate concentration from his numerous transfusions. The patient also had ammonium intoxication and active hepatic necrosis, as judged by the cholemic odor, increasing fever, and profound coma.

In view of the desperate situation and the almost hopeless prognosis, a number of additional therapeutic efforts were made. The patient was given Premarin Intravenous, calcium gluconate and massive doses of antibiotics. Cortisone acetate (100 mg. every six hours intramuscularly) also was started with several objectives in mind, *viz*, a possible beneficial vascular effect, the minimizing of acute hepatic necrosis, and the possibility of reducing intrahepatic edema, thus leading to partial decompression within the portal venous system.

During the next eight hours the gastro-intestinal hemorrhage abated considerably. Even though only two additional transfusions were given, the hemoglobin level (which previously had been 9.1 and 9.8 Gm. per 100 ml. respectively, with corresponding diminutions in the hematocrit) rose the next day to 13.5 Gm. per 100 ml., with an hematocrit of 44 per cent. The patient then experienced intermittent generalized convulsive seizures. These were attributed to the combination of cerebral hypoxia, hyperammonemia, respiratory alkalosis, and possibly hypocalcemia, hypoglycemia, magnesium deficiency, or mild overhydration. With the administration of sodium luminal in small amounts, calcium gluconate intravenously and packed red blood cells, along with fluid restriction, the convulsions disappeared by the following day (magnesium sulfate temporarily being withheld). The dosage of cortisone subsequently was reduced to 50 mg. every six hours, and then every twelve hours. By this time, he was receiving supplementary potassium and Gelusil orally. During this period, a profound improvement had taken place in the patient's mental status.

Two days later, prednisolone (5 mg. every six hours) was started, the dosage subsequently being reduced to 2.5 mg. every six hours. The temperature remained normal thereafter. The stools were still dark, but the hemoglobin level was maintained at 13.3 Gm. per 100 ml., and the hematocrit at 39 per cent. The serum electrolyte and bilirubin levels returned to normal. The patient then fared well enough to be sent to another medical center where a portacaval shunt was successfully performed. Thereafter, he was productively engaged in an executive capacity for more than three years. His regimen consisted of complete abstinence from alcohol, an adequate diet with moderate quantities of protein, multivitamins, and intermittent injections of vitamin B_{12}. Neomycin (orally) also was added after a bout of ammonium intoxication (precipitated by one tablet of promazine). Blood ammonia levels after clinical recovery were 0.8 mg. and 0.5 mg. per 100 ml., respectively (normal up to 0.15 mg. per 100 ml).

This patient also received estrogens intravenously on numerous occasions during the postoperative period because of frequent (one to four times weekly) and profuse nosebleeds which would respond promptly and predictably. Repeated attempts to control and prevent the epistaxis (with the inherent risk of clinical ammonium intoxication) by means of cauterization proved unsuccessful. On no occasion was there any evidence of significant gynecomastia or weight increase following prolonged, intermittent intravenous therapy with estrogens. On the other hand, estrogens could not be tolerated orally by this patient owing to the sudden appearance of marked edema.

In June 1960, he experienced a bout of massive hematemesis without pain or apparent precipitating cause. The hematocrit was 26 per cent, hemoglobin level 8.2 Gm. per 100 ml., and the erythrocyte count 2.8 million per cu. mm. Symptoms of progressive ammonium intoxication developed during the ensuing twelve hours. A regimen was promptly started

which included dexamethasone intramuscularly (4 mg. every six hours), Premarin Intravenous (20 mg. at once, 20 mg. in another hour, and thereafter every six hours), an oral antacid preparation, and 1.0 Gm. of neomycin orally every six hours. He was given glucose solutions parenterally with supplementary vitamins and electrolytes; 2 units of whole blood also were administered. With this program, the hematemesis did not recur, and there was no further evidence of active gastro-intestinal bleeding during the remaining six days of hospitalization.

Thereafter, the serum nonprotein nitrogen level rose progressively to 96 mg. and 133 mg. per 100 ml. The prothrombin time subsequently was found to be 23 seconds (control, 15 seconds). A repeated prothrombin determination gave the same value, which remained unaltered by a 10-mg. dose of vitamin K_1 oxide. The dosage of dexamethasone was progressively reduced over the ensuing three days and discontinued on the fourth hospital day. Repetition of the upper gastro-intestinal x-ray series failed to demonstrate esophageal varices or any pathologic condition in the stomach. The patient continued to improve, and at the time of discharge was told to continue a low-protein diet, antacid medication, and neomycin orally.

Case # 2

A. G., a 52-year-old female, was first seen in May 1956 with increasing abdominal distention, weakness and progressive jaundice of several months' duration. She had been consuming large amounts of alcohol for many years. The diagnosis was chronic cirrhosis with decompensation. In spite of repeated admonitions to the contrary, she continued to drink. She was admitted to the hospital with marked ascites and evidence of impending hepatic coma. With a program of abstinence from alcohol, supportive measures, judicious diuretic therapy and salt restriction, the patient fared very well for the ensuing year. She had fairly severe anemia that could not be attributed to overt loss of blood from the gastro-intestinal tract. This responded well to a nutritious diet, parenteral vitamin B_{12}, and several transfusions of packed red blood cells.

When seen in August 1957—following her resumption of alcohol—she had experienced massive melena and hematemesis. There was evidence of a profound anemia. Physical examination revealed mild icterus, tachycardia, some distention of the abdomen with a markedly enlarged nontender liver, and an early coarse tremor. Following three transfusions, she continued to bleed and remained as anemic as previously. Premarin Intravenous was started in a dosage of 20 mg. daily for two days. Within twelve hours after the first injection, there was no further overt clinical bleeding. Thereafter, a striking improvement occurred in her appetite, general appearance and mental attitude. There was no evidence of fluid or electrolyte retention during this time.

During the next year, the patient was admitted to the hospital twice with massive gastro-intestinal hemorrhage, under virtually the same set of circumstances. Each time, her initial appearance was more shocking. During her fourth admission, ammonium intoxication was evident clinically, with the classic tremor and lethargy. On each occasion, the prompt institution of intravenous estrogen therapy and cortisone acetate for a period of several days rapidly brought the gastro-intestinal hemorrhage under control for the duration of the hospital stay—until she again resumed drinking.

The patient was readmitted for the last time on September 11, 1958, with recurrent hematemesis, jaundice, marked ascites and impending ammonium intoxication. Shortly after admission, however, irreversible shock and death intervened. An autopsy confirmed the presence of Laennec's cirrhosis of the liver with esophageal varices and multiple minute erosions of the gastric mucosa.

Case # 3

J. P., a 61-year-old mechanic, was admitted to the hospital with a history of having been well until five days previously, when he began to notice tarry stools followed by black vomitus on several occasions. The bleeding had come after heavy week-end drinking. He

experienced extreme weakness—particularly on attempting to stand—prior to the more overt bleeding. There had been no previous known episode of gastro-intestinal bleeding or jaundice. His past history was significant only in his having been a heavy smoker and having undergone a cholecystectomy.

Physical examination on admission revealed a well developed male of the approximate stated age, with profound pallor. The pulse was 82 and full. The blood pressure was 110/76 mm. Hg. Moderate emphysema was present. The abdomen was slightly distended. The liver was nontender and palpable approximately three fingerbreadths below the costal margin in the right upper quadrant and four fingerbreadths in the epigastrium. No palpably or percussibly enlarged spleen or other abdominal masses were noted. No ascites, spider angiomata, or evidence of extensive collateral circulation could be found. The erythrocyte count was 2.14 million per cu. mm., hemoglobin level 6 Gm. per 100 ml., hematocrit 19 per cent, and leukocyte count 15,000 per cu. mm.

The patient obviously had had a massive gastro-intestinal hemorrhage, but it could not be ascertained on admission whether this was due to alcoholic gastritis, acute peptic ulceration, or bleeding from esophageal or gastric varices associated with portal hypertension in the presence of longstanding cirrhosis. Active bleeding continued. During the next thirty-six hours, he was given 5 units of whole blood, 3 injections of Premarin Intravenous (20 mg. at approximately ten-hour intervals), and cortisone acetate (50 mg. every eight hours intramuscularly). Within the first overnight period of observation, his condition had improved considerably, with no further evidence of active gastro-intestinal bleeding. A first-stage ulcer diet was started. Subsequently he was given small amounts of an antacid-anticholinergic preparation. There was a continued rise in the blood indices. The stools progressively appeared more normal. Liver function studies performed in the ensuing days revealed normal values for thymol turbidity, cephalin flocculation, and serum transaminase, total protein, and albumin-globulin levels. Bromsulfalein retention (at forty-five minutes) was 7 per cent. An upper gastro-intestinal x-ray series demonstrated an active duodenal ulcer. The patient's course thereafter was completely uneventful.

PLAN OF DISCUSSION

In attempting to explain the salutary effects of estrogen-adrenocortical therapy in the control of gastro-intestinal hemorrhage, the action of each agent will be first considered separately, followed by an analysis of estrogen therapy in the presence of liver disease and a consideration of certain pertinent clinical problems in the management of gastro-intestinal hemorrhage associated with cirrhosis.

THE HEMOSTATIC ACTIONS OF ESTROGENS

Estrogens, both orally and intravenously, have proved to be of value in the management of certain hemorrhagic disorders that had proved difficult to control by other measures. In my experience, these situations include bleeding (either spontaneously from the gastro-intestinal, genito-urinary and respiratory tracts, or following dental extraction) during long-term anticoagulant therapy; hemorrhagic telangiectasia; extensive steroid-induced purpura; and recurrent intraocular hemorrhage in cases of diabetic retinopathy (10, 15). The literature also contains a number of reports concerning the intravenous use of estrogens for effective control of functional uterine bleeding, tubercular hemoptysis, traumatic hyphema, delayed post-traumatic hemorrhage, and bleeding following tonsillectomy, prostatectomy or ophthalmic surgery (16–23). Other reports cite the control use of estrogens intravenously for suppression of otherwise uncontrollable massive hemorrhage following dental extraction in a case of hemophilia (24), and in cases of fibrinolysis during and after surgical operations (25, 26).

There is still a paucity of clinical and experimental information concerning the mechanism of action of this "physiologic hemostat." Conjugated estrogens exert their influence in various spheres of the blood clotting mechanism, but most notable is their action on and about the capillary bed. It was demonstrated as far back as 1933 that abnormal bleeding times in newborn infants could be lowered by parenteral administration of crystallized estrin (Theelin) (27). The rapid increase in concentration of estrogens was probably an essential factor in promoting coagulation of the blood.

One mechanism of action which may account for the *enhanced coagulation* is related to the sharp rise in Factor V (plasma Ac-globulin, pro-accelerin, labile factor) following intravenous infusion of estrogenic steroids (28). This change was observed in dogs within the first fifteen minutes after infusion, reaching a peak in approximately ninety minutes, and returning to the normal level by four hours. An increase in the prothrombin concentration and a decrease in the antithrombin activity of plasma was also noted following intravenous infusion of estrogens into dogs (28).

Detailed studies in humans specifically relating to the effect of conjugated estrogens (intravenous) on the individual factors involved in the coagulation process have been carried out recently (29). The increase in Factor V was corroborated, but no demonstrable change in the prothrombin time, the prothrombin content, Factor VII, the bleeding time, the clotting time, or the amount of clot retraction could be detected. In patients with coronary heart disease who had begun to bleed because of hypoprothrombinemia during long-term anticoagulant therapy the author usually could not detect significant alterations in the concentration of prothrombin following intravenous administration of conjugated estrogens (10). It should be pointed out, however, that values for Factor V in the dog normally tend to be high, whereas those in the human (10–15 units per ml.) are among the lowest for all the species tested (30). Accordingly, a decrease of only a few units in man might have an important bearing upon bleeding in certain situations; conversely, any agent that can induce an elevation of Factor V concentration might prevent or control bleeding (28).

Additional evidence that estrogens can influence the coagulation mechanism stems from the observation that intravenous infusion of estrogens produces a definite decrease in the prolonged clotting time induced in dogs suffering from an acute radiation syndrome (31). Such an effect was observed between thirty minutes and one hour following injection.

The use of estrogens intravenously combined with cortisone or prednisone has proved of value as a supplement to intravenous infusion of fibrinogen and transfusion of packed red blood cells in the control of serious hemorrhagic complications associated with fibrinolysis, particularly in patients with cancer of the prostate (25, 26). The inhibition of fibrinolytic activity by estrogens is reflected in the rise of blood fibrinogen levels (32a).

Evidence recently has been presented by Mellette and others for a vitamin K-mimetic action of estrogens (32b). It was observed that female rats are more resistant to the development of dietary vitamin K deficiency than their male counterparts, especially during early adulthood. Either castration or the admin-

istration of estrogens to male rats improved prothrombin levels and lowered the mortality, whereas castration of the female or treatment with testosterone exerted an opposite effect. The greater mortality in male rats following a single large dose of warfarin sodium also could be reduced by previous or concomitant adminstration of estrogenic substances. (No significant change in Factor V was demonstrable.) Mellette further noted that both vitamin K_1 and menadione tend to increase uterine weight and cornification of the vaginal epithelium in castrated mice—effects that are characteristic of estrogenic hormones (32b).

Abnormal results in the over-all tests for clotting and in those designed to measure factors contributing to thrombin formation and fibrin deposition have been demonstrated in patients with gastro-intestinal hemorrhage (8). Such changes may be of little significance with reference to clinical hemostasis, however, even in the presence of severe liver disease (33). Furthermore, even though the platelets may become markedly depressed during massive gastro-intestinal hemorrhage and for several days thereafter in patients with and without liver disease, they remain adequate for purposes of hemostasis (34). These observations add further support to the salutary vascular action of estrogens.

Estrogens also exert an appreciable *influence on the capillary bed*, as indicated by the following observations:

1) Suppression of recurrent epistaxis and gastro-intestinal bleeding in hemorrhagic telangiectasia has been observed both cyclically in relationship to the menses and following either oral or parenteral administration of estrogens (1, 35, 36).

2) In many instances, massive spontaneous epistaxis not controllable by anterior and posterior packing, administration of vitamins C and K, ice packs, cauterization or thrombin and fibrin foam, responds promptly to intravenous estrogen therapy (37). Following the estrogen-induced arrest of epistaxis, the open vessels can readily be seen, as can the change from a congested cyanotic membrane to a more normal hue (1, 20).

3) Intravenous infusion of estrogens (one to four times daily) has controlled bleeding for more than four months in one of our patients—a 21-year-old male with severe aplasia of the marrow who bled profusely from virtually every cutaneous and mucosal site in his body when this therapy was omitted (10). Furthermore, each of three uncomplicated bone marrow aspirations was performed half an hour after the intravenous injection of Premarin—in one case when the platelet count was less than 11,000 per cu. mm., the bleeding time more than twenty minutes, and clot retraction virtually nil at three hours.

4) Another noteworthy feature in some cases of cirrhosis with massive gastro-intestinal hemorrhage is the frequency with which epistaxis and other forms of bleeding (in the absence of marked telangiectasia) occur subsequently, and the repeated prompt response of such episodes to intravenous administration of estrogens. For example, a 59-year-old female with advanced primary biliary cirrhosis who had undergone a portacaval shunt for massive esophageal bleeding continued to have repeated nosebleeds every three to five weeks in spite of local measures. These responded promptly to intravenous estrogen therapy for more

than a year. In patients with cirrhosis who are on the verge of ammonium intoxication (*e.g.*, the case just cited and Case 1), the ability to check epistaxis and lessen the amount of blood swallowed may prevent precipitation of an attack.

Perhaps the most significant studies explaining the hemostatic vascular action of estrogens are those dealing with the effect of estrogens on tissue acid mucopolysaccharides. (The cement substance of the capillaries is a mixture of acid mucopolysaccharides, whereas the capillary sheath is almost pure hyaluronic acid. The chief acid mucopolysaccharides are hyaluronic acid and the 3 chondroitin sulfates, A, B and C.) By means of colloidal iron and toluidine-blue stains, Schiff and Burn (38) repeatedly demonstrated a progressive change of the mucopolysaccharides from the sol state to the gel state in the tissues of hamsters, monkeys and man following intravenous infusion of estrogens; this change lasted for several hours. Such an alteration in the ground substance appears to be caused by an increase both in the quantity and polymerization of the mucopolysaccharides about the small blood vessels and in the arteriole walls, an effect that occurs equally in males and females. It is possible that estrogens stimulate the production of glucuronic acid (an integral part of both hyaluronic and chondroitin sulfate molecules), which in turn enhances the synthesis of more mucopolysaccharides (38). Estrogens intravenously may also induce an appreciable increase in the serum hyaluronic acid level (39).

Estrogens may enhance the resorption of hemorrhagic residues by an effect upon a spreading factor (40). There is evidence based on the inhibition of hyaluronidase wheals that estrogens given intravenously act on the ground substance to limit the activity of hyaluronidase (39). Other possible actions of estrogen therapy on the vascular bed include a serotonin-like effect and the neutralization of a vascular toxin (20).

Estrogens act catalytically and in low concentration at critical levels of cell metabolism in a wide variety of tissues. For example, diethylstilbestrol strongly inhibits diphosphopyridine nucleotide oxidation normally carried out by enzymes from a variety of mammalian tissues, tumors and micro-organisms. The site of this inhibition has been localized in skeletal muscles to DPNH cytochrome C reductase (41). Since the nucleotide specific electron transport pathways represent critical control points in metabolic reactions, this inhibitory effect of estrogens and other hormonally active steroids enables small amounts to exert a significant metabolic influence, even in tissues devoid of steroid enzymes.

Another interesting action of estrogenic substances in catalytic oxidation is the effect upon plasma copper transport and ceruloplasmin (42). The bonding forces holding the 8 copper atoms of ceruloplasmin are divided between 4 which are held by relatively weak forces (readily removed by chelating agents such as versene) and 4 that are firmly bound. In both cases the labile and stable copper atoms are associated with reactive sites capable of catalytic oxidation of catechol and other amines and serotonin; the labile copper atoms also are involved with catalyzing the oxidation of ascorbic acid. In normal volunteers and in certain cancer patients, it was found that the ceruloplasmin level rose from two- to

eight-fold following administration of stilbestrol. When the drug was discontinued, there was a return to the initial plasma levels.

Hench has speculated upon the important clinical and pathogenetic potentialities of major cortisone "ebb-tides" as related to the onset, exacerbation and renewal of certain rheumatic and collagen inflammations (43). It is possible that there are premonitory estrogen "ebb-tides" related to the pathogenesis of certain cyclic hemorrhagic disorders of the gastro-intestinal tract and other organs. The cyclic periodicity of postoperative hemorrhage and of bleeding peptic ulcer has received sporadic attention for many years (44). An increased tendency to bleeding from hereditary telangiectasia is evident prior to the menstrual period, after the menopause, and following ovariectomy (45).

Jacobson (1, 20) has advanced the concept that spontaneous hemorrhage with no evidence of underlying or previous organic disease in the gastro-intestinal tract or elsewhere may represent a state of hormonal imbalance. This tenet is based largely upon the following factors: 1) the blood is usually normal, insofar as can be determined; 2) the disorder is episodic; and 3) it responds to treatment with hormones, principally estrogens. The period of altered metabolic activity that precedes the bleeding by several days or even weeks has been likened to the premenstrual period with its rapid hormonal changes. Hot flushes or tension and emotional hyperactivity are often noted prior to the bleeding in cases of spontaneous hemorrhage, and this may have some physiologic significance. The possibility that there is a toxin with a peculiar affinity for the vascular system (comparable to the so-called "menotoxin" demonstrated in the circulating blood of menstruating women) (46, 47), has also been postulated on the following basis: 1) the episodic nature of spontaneous bleeding; 2) the multiplicity and variety of the lesions in the stomach, the nose, the hemorrhoidal plexus and elsewhere; 3) the disproportion between the size of the lesions and the amount of blood escaping from them; and 4) and the rapidity of their appearance and disappearance.

THE RATIONALE OF ADRENOCORTICAL STEROID THERAPY IN CIRRHOTIC HEMORRHAGE

There are several possible explanations for the beneficial effect of adrenocortical steroids in the management of massive gastro-intestinal hemorrhage in patients with cirrhosis:

1) Cortisone and corticotropin decrease capillary permeability and reduce the prolonged bleeding time in certain hemorrhagic states, most notably "pseudohemophilia" (48).

2) Corticosteroids induce hypercoagulability of the blood. This effect has been attributed variously to thrombocytosis and to decreased plasma fibrinolytic activity (possibly mediated through the inhibition of the action of serotonin in promoting fibrinolysis) (25, 26, 49).

3) Corticosteroids favorably influence associated hypersplenism and thrombocytopenic purpura (50).

4) Cortisone therapy exerts a beneficial effect upon the massive gastric bleeding stemming from increased capillary fragility associated with gastric erosions (51).

5) Corticosteroids reduce the acute hepatocellular damage that is frequently superimposed upon pre-existing cirrhosis. This in turn causes partial decompression of the portal hypertension. (The degree of portal hypertension is influenced not only by the extent of periportal fibrosis in the interlobular spaces, but also by the narrowing and obliteration of the smaller portal channels as a result of regenerated hepatic nodules or superimposed acute inflammatory changes.) Medical therapy reduces the elevated portal pressure in cirrhosis when it is due chiefly to fatty metamorphosis, inflammation or liver-cell necrosis (52). There is ample evidence that steroid therapy per se, rather than the concomitant rest and diet, dramatically reduces the serum bilirubin level, bromsulfalein retention, the spider nevi, and the amount of fatty and inflammatory infiltration within the liver (as observed from serial biopsy studies in patients with both acute and chronic liver disease).

6) Cortisone and its analogs have proved beneficial in occasional cases of hepatic coma (53).

7) Cirrhotic patients may suffer from relative adrenal insufficiency with reference to the secretion of cortisol and corticosterone because they metabolize cortisol at a slower rate even though they maintain normal plasma cortisol levels under basal conditions (54a). A homeostatic mechanism is mediated through the liver, pituitary and adrenals which can decrease the synthesis of these hormones when the rate of cortisol removal by the cirrhotic liver is impaired. (The metabolic defect may reside in a low hepatic activity of the specific TPNH-dependent enzyme that catalyzes reduction of the 4,5 double bond.)

8) Adrenocortical steroid therapy provides nonspecific support of the cardiovascular system and enhances the patient's appetite and sense of well-being.

9) It has been suggested by Lillehei that the efficacy of adrenocortical steroids in these studies is attributable in part to their protecting the already hypoxic liver against the further insult of hemorrhagic hypoxemia—comparable to the salutary effect upon the ischemic intestinal wall he has observed with their use (54b).

INTERRELATIONSHIPS BETWEEN ADRENOCORTICOSTEROID AND ESTROGEN METABOLISM

Several recent reports indicate that administration of estrogen can influence adrenocortical steroid metabolism. For example, oral administration of estrogens elevates the plasma level of free 17-hydroxycorticosteroids, delays the plasma clearance of exogenous cortisol, and reduces the urinary excretion of conjugated 17-hydroxycorticosteroids (55). Urinary corticosteroids are decreased about 30 to 50 per cent after two to three weeks of estrogen administration (0.5 mg. of ethinyl estradiol daily) in both males and females, largely representing a decrease in the rate of synthesis of cortisol and corticosterone (56). Estrogens also decrease

the excretion of other urinary steroids of gonadal and adrenal origin in males and females, including androsterone, etiocholanolone, dehydroisoandrosterone, 11-oxyketosteroids, ketogenic steroids and pregnanetriol (57).

These effects have been attributed in part to the induced increase in cortisol-binding to transcortin. (Transcortin is a corticosteroid-binding protein present in low concentrations in the plasma. Cortisol is bound to transcortin 6,000 times more strongly than it is to albumin, the other circulating hormones being bound either weakly or not at all by transcortin. The transcortin capacity is greatly increased both during pregnancy and when estrogen therapy is continued.) Determinations of both total and protein-bound 17-hydroxycorticosteroid concentrations in the plasma have revealed that the elevation in Cushing's syndrome is due almost entirely to an increase in the nonprotein-bound fraction, that the elevation in estrogen-treated males without signs of Cushing's syndrome is due entirely to an increase in the protein-bound fraction, and that the levels of both protein-bound and nonprotein-bound 17-hydroxycorticosteroids are increased during the third trimester of pregnancy (58). These studies suggest that the nonprotein-bound plasma fraction is the immediately active form of cortisol.

Competitive inhibition between cortisol and estrogens at an enzymatic level is likely since the defect in biotransformation can persist for weeks following discontinuance of estrogen therapy. This may involve the level of one of the co-enzymes (TPNH) or of the TPNH-linked steroid dehydrogenases in the liver that are necessary for enzymatic inactivation of these steroids. For example, the predominant initial reaction in the metabolism of cortisone is a reduction of the C-11 ketone to an 11-hydroxy function (cortisol).

The absence of signs of Cushing's syndrome in patients receiving estrogens for long periods of time is attributed to the fact that the rise in plasma hydrocortisone levels is due not to an increased secretion and consequent rise in the tissue levels of hydrocortisone, but rather to diminished transformation of hydrocortisone to its metabolites (*e.g.*, tetrahydrocortisone) and retention of the hormone within the intravascular or extracellular fluid compartments (59). The normal levels of plasma free 17-hydroxycorticosteroids in patients with cirrhosis is in contrast with the increased levels in patients receiving estrogens. This discrepancy has been attributed to the change in steroidal distribution achieved by estrogens, in which tissue cortisone levels fail to rise to the same degree as the plasma levels. The pituitary-adrenal feedback mechanism then may fail to respond sufficiently to restore the plasma 17-hydroxycorticoid levels to normal (59). Such an explanation receives further support by the lack of Crooke's changes in the pituitary basophil cells of patients with carcinoma of the prostate receiving long-term estrogen therapy (59).

Other evidences of the interrelationships between adrenocortical and estrogenic metabolism include the following: *a*) cortisone can be converted directly to phenolic estrogens (particularly the 11-oxygenated estrogens) in human subjects (60); *b*) the excretion of large amounts of estrone, estradiol and estriol, comparable to the quantities observed in late pregnancy, has been observed in a

male patient with a feminizing adrenocortical carcinoma (61); *c*) estrogen therapy in itself can suppress the urinary excretion of 17-ketosteroids and decrease both the facial hirsutism and ovarian enlargement in some women with virilism (62); *d*) a statistically significant decrease occurs in the response of these urinary steroids to corticotropin stimulation when estrogen is administered for five days preceding an infusion of ACTH (57); *e*) a definite influence on the intermediary metabolism of exogenous cortisone is exerted by the presence of ovaries in adrenalectomized breast cancer patients (63, 64); and *f*) the significantly lower excretion of estrone and estradiol-17β induced by the administration of cortisone during the follicular phase of the menstrual cycle (65).

ESTROGEN THERAPY AND LIVER DISEASE

In the light of these favorable therapeutic experiences entailing the use of estrogens, the prevalent fear that a damaged liver is unable to inactivate or to excrete large doses of estrogen requires closer scrutiny. A number of phenomena associated with hepatic insufficiency (*e.g.*, testicular atrophy, marked hyperplasia of the breasts, decreased libido and potency, decreased body and axillary hair, menstrual irregularities, telangiectasia, and "liver palms") have been attributed to the impaired ability of the damaged liver to inactivate or to excrete endogenous estrogens (66). The following impressive array of observations in the literature are presented as evidence that there are clinical and pathologic counterparts of such impaired inactivation or excretion of steroids by the severely damaged liver:

1) Extension of spider angiomas in the cirrhotic patient following the administration of estrogen (67).

2) The excretion of appreciable amounts of free estrogen and often no combined estrogen by patients with chronic parenchymal hepatic disease, in contrast with the normal excretion of virtually no free estrogen and only 10 to 12 μg. of total estrogen per twenty-four hours (68).

3) The occurrence of gynecomastia in patients with liver disease who are excreting free estrogen.

4) The recovery in urinary extracts of up to 86 per cent of estradiol injected into cirrhotic males (69).

5) The significant increase in estrogen excretion during the acute phase of infectious hepatitis (70).

6) The postmortem findings of severe testicular atrophy, metaplasia of the prostatic glandular and ductile epithelium, and marked hyperplasia of the breasts (along with a decreased incidence of benign prostatic hypertrophy) in patients with cirrhosis (66, 71).

7) The resemblance between the estrogen-induced disturbance in the transformation of hydrocortisone to certain metabolites and that seen in patients with cirrhosis (72).

Although impaired metabolism of the biologically active estrogens appears to explain many of the aforementioned clinical findings in patients with chronic liver disease, this thesis has not been accepted universally. The newer chemical

methods for measuring the 3 important urinary estrogens (estrone, estradiol-17β, and estriol) are more sensitive than the previous technics for the bio-assay of estrogens, and with their use it has been observed that the total excretion of estrogens is *not* increased in most patients with chronic liver disease, including those with spider nevi, erythema and ascites (73). Furthermore, there is no consistent correlation between the increased excretion of these substances and the occurrence of gynecomastia or the degree of liver malfunction (65). A fall in estrogen secretion (particularly in the ratio of free to total estrogens) may parallel improvement in liver function after estrogen is administered to a cirrhotic patient with gynecomastia (74). Others have found that elevated estrogen excretion occurs in only about one-third of patients with cirrhosis, and that there is no consistent correlation between estrogen excretion, spider telangiectasia, gynecomastia, or palmar erythema (77). It has been pointed out that a deficiency, rather than an excess, of estrogens could account for the uterine and mammary atrophy, the oligomenorrhea or amenorrhea, and the decreased axillary hair in women with advanced liver disease (77)—perhaps on the basis of a pituitary depression, independent of hyperestrogenism and largely related to nutritional factors. Other explanations relate to an altered androgen-estrogen ratio in cirrhosis, impaired inactivation of estrogens by a deficiency of vitamin B complex, and protein depletion (78). In patients with chronic liver disease treated with progesterone for twenty-four to thirty days, there is little or no interference in the metabolism of progesterone to pregnanediol, as indicated by the increased excretion of pregnanediol in the urine (75). Perhaps 16α-hydroxyestrone or one of the biologically active estrogen metabolites not yet studied in detail may be increased in liver disease and could account for such manifestations (65).

It should be emphasized that the liver tenaciously retains its ability to inactivate estrogens. At times, this function even outlasts its capacity to synthesize urea (76). The estrogens recovered in the urine are usually conjugated as glucuronates and sulfates. (The daily urinary excretion of estrogen by normal men, expressed in terms of estrone, varies between 5 and 25 μg.; in women it ranges from a minimum of 5–20 μg. to a maximum of 60-100 μg. in midcycle and premenstrually.) Although more than 90 per cent of exogenous natural estrogen is degraded in all species, there are marked species differences in the hepatic inactivation of estrogens. Endogenous estrogen levels in pregnant women with severe hepatitis generally are normal—further evidence that the acutely diseased liver can inactivate large amounts of hormone (65).

No complications were observed in this series that could be attributed specifically to inability of the liver to handle exogenous estrogens administered intravenously. The significant and sustained retention of sodium chloride and water in patients with disease of the liver (particularly with ascites or a marked disturbance of the hepatic circulation) following the *intramuscular* injection of potent estrogenic substances appears to be due to: 1) decreased hepatic inactivation of the hormone, which in turn is dependent more upon the disturbance in hepatic circulation than upon the amount of hepatocellular damage; and 2) a probable direct action of the estrogen on the renal tubules, since it does not appre-

ciably affect the renal clearances of either mannitol or para-aminohippuric acid (79). Salt and water retention can also be induced by intramuscular injection of estradiol in cases of constrictive pericarditis or cardiac failure, but not in cases of peripheral venous obstruction, the nephrotic syndrome, or low plasma albumin without renal disease (79c). Such estrogen-induced fluid retention is largely independent of the influence of aldosterone.

RELATED PROBLEMS IN THE DIAGNOSIS AND TREATMENT OF GASTRO-INTESTINAL BLEEDING IN CIRRHOTIC PATIENTS

A number of important diagnostic considerations influencing treatment should be entertained before concluding that bleeding in a patient with cirrhosis is due to esophageal or gastric varices. A concomitant peptic ulcer, erosive gastritis, the Mallory-Weiss syndrome, hiatal hernia, or drug-induced ulceration merit particular attention. The differential diagnosis has been reviewed by the author (80). Although the degree of bromsulphalein retention is generally a safe and reliable diagnostic guide, it is well to bear in mind that abnormal BSP retention can occur in the presence of a normal liver as a result of anoxia caused by loss of blood. While elevation of the arterial blood ammonia level suggests that a patient may have esophageal varices, this sign cannot be relied upon since it can occur in the presence of gastro-intestinal hemorrhage from various causes (3). The cessation of bleeding following institution of balloon tamponade is not diagnostic of variceal bleeding inasmuch as it may be a peptic ulcer that has stopped bleeding; on the other hand, hemorrhage can continue following tamponade for esophageal varices, either from a gastric varix or a concomitant peptic ulcer.

Even when esophageal varices have been demonstrated in a case of cirrhosis, one cannot assume that massive hemorrhage stems from this source. For example, large areas of the superficial gastric mucosa can suddenly exfoliate (so-called erosive gastritis) and cause massive hemorrhage, only to heal promptly. (This situation has been likened to exfoliation and restitution of the endometrium.) The constant dynamic changes in esophageal varices—waxing and waning although the hepatic disease remains unchanged—command increasing attention. Continual alterations have been observed in the diameter and extent of the varices, and even complete disappearance (81). These variations are of great importance in patients with esophageal varices who are candidates for portacaval shunt operations; in these cases a second preoperative examination may reveal complete disappearance of the varices. Palmer (81) has pointed out that there is often no correlation between the level of the portal venous pressure and the diameter or extent of the varices. He notes that varices have their inception during the precirrhotic stages of the progressive hepatic lesion and *before* perilobular fibrosis has developed.

Child and Donovan (82) made the following pertinent observations referable to hemorrhage from esophageal varices in patients with portal hypertension: 1) although a frank ulceration or tear generally can be demonstrated, the site of hemorrhage is not demonstrable in 10 per cent; 2) the hemorrhage cannot be validly explained on the basis of increased pressure since there is no bleeding in

the other areas of the portal bed, nor can it be explained on the basis of ulceration secondary to esophagitis since there are no symptoms of esophagitis and very little evidence of incompetency of the esophagogastric sphincteric mechanism; and 3) it is the consensus that neither thrombocytopenia nor any other hemorrhagic diathesis initiates the bleeding (82).

The hazards of administering large doses of vitamin K or K_1 to patients with liver disease and hypoprothrombinemia have been appreciated only recently and should be emphasized (6). Following the administration of 72 mg. of vitamin K (Hykinone) or 50 mg. vitamin K_1 (Mephyton), it was found that patients with advanced liver disease manifested either no significant rise in prothrombin activity or a further decrease.

There are several favorable reports pertaining to the use of posterior pituitary extract (10–20 units) in the control of esophageal variceal bleeding (83–85). In 11 of 13 patients with cirrhosis and portal hypertension, a fall in the wedged hepatic vein pressure ranging from 19 to 59 per cent of the original value was observed during infusion of 20 to 40 units of vasopressin per hour (85), along with a decrease of from 17 to 63 per cent in the hepatic blood flow. The explanation offered for this response was the lowering of portal pressure caused by temporary splanchnic vasoconstriction and reduced inflow into the portal bed. Unfortunately, in 5 of 8 patients with esophageal bleeding initially controlled by this means, the hemorrhage recurred and there was a diminished response to vasopressin (84). Although not employed in the present study, vasopressin therapy would seem to be a useful supplement to the combined administration of estrogens (intravenously) and adrenocortical steroids (intramuscularly) in the bleeding cirrhotic patient.

General hypothermia and local gastric hypothermia have been advocated as measures to control bleeding varices, particularly preoperatively (86, 87). Combined steroid therapy may potentiate such treatment, as suggested by the results of our current studies on the management of severe subarachnoid bleeding and brain-stem infarction (88, 89).

Should variceal hemorrhage continue in spite of all conservative measures, emergency ligation of the varices or immediate portacaval shunt may be in order; many authorities favor the former procedure (3). In the occasional case of variceal hemorrhage in portal hypertension due to an extrahepatic cause, however, the postoperative course may be complicated by gradual deterioration of hepatic function and clinical evidence of ammonium intoxication.

SUMMARY

The use of estrogens intravenously combined with adrenocortical steroids parenterally is of distinct benefit in the management of massive gastro-intestinal hemorrhage associated with cirrhosis of the liver. This regimen proved effective after conservative measures had failed in 5 cirrhotic patients, one of whom had primary biliary cirrhosis.

In alcoholic patients with hepatomegaly and gastro-intestinal hemorrhage, such therapy proved beneficial even when a peptic ulcer, rather than varices, was the only pathologic lesion demonstrable by x-ray examination.

The pharmacology and the rationale and limitations of this combined hormonal therapy are discussed. Its value in the treatment of hemorrhage of obscure origin in cases of cirrhosis and the supplementary role of other therapeutic techniques are also considered.

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TREATMENT OF OVERWEIGHT PATIENTS WITH CHORIONIC GONADOTROPIN

PHILLIP LEBON, F.R.C.S.*

London, England

Surgeons who have to operate on the obese are likely to welcome a safe and effective way to procure pre- and postoperative weight reduction. Simeons (1) noted that the distribution of excess fat in such patients resembled that in Fröhlich's syndrome, and he reported good results from treatment with chorionic gonadotropin and a low calorie diet. What particularly impressed him was that his patients readily lost weight without becoming haggard about the face.

Neither in this nor in a later paper (2) did Simeons suggest the applications of his method to the problems of the surgical treatment of the obese; but since it seemed to offer encouraging possiblities, his technique has been adopted in a series of 63 cases.

METHOD AND RESULTS

All of the 63 patients were ambulant and continued full-time work throughout treatment. They were given 125 units of chorionic gonadotropin a day by deep intragluteal injection, and were maintained for periods ranging from seventeen to forty consecutive days on a 500-calorie, fat-free diet containing 200 grams of protein. The body weight was carefully watched during treatment; but since the investigation concerned only controlled weight reduction either before or after the operation, there was no follow-up of the weight.

Of the 63 patients, 43 were females and 20 males; 44 of them completed forty consecutive days of treatment, and the other 19 were treated for twenty-one consecutive days. The mean weight loss of the 44 patients who had taken 40 injections was 25 pounds. However, 6 of them did not diet conscientiously and the poor results lowered the general average. If they are excluded, the mean weight loss was 28 pounds. The average loss in patients who undertook the 21-day treatment was 16 pounds.

Of the 63 patients, 18 were surgical cases. Two had their operations before, 5 during, and 9 after treatment. The other 2 are awaiting operation (see Table 1).

DISCUSSION

Though no statistical conclusions can be drawn from this limited series, the findings and the manner in which they were obtained are most promising. None of the patients felt hungry or weak. The best results were achieved when the patient co-operated completely, but even those who dieted irregularly lost weight more readily than by any method of treatment previously tried. Many patients who were previously refractory to other regimens now lost weight for

* *Address:* 20, Gt. Cumberland Place, W.1, London, England.

TABLE 1

Data on Treatment of 63 Patients with Chorionic Gonadotropin

Patients		Consecutive Days of Treatment	Overweight (lbs.)	Weight Loss (lbs.)	Remarks
Case No.	Age (yrs.)				
			Females		
1	74	40	79	28	Hypertensive heart failure.
2	59	40	22	7	Alcoholic; hiatus hernia.*
3	37	40	34	17	Irregular dieting.
4	57	40	28	21	Depressed.
5	23	20	8	12	
6	48	40	84	32	
7	19	40	54	30	
8	48	30	42	17	
9	56	40	42	24	Alcoholic.*
10	31	40	28	26	Hypertensive; 4 terminations of pregnancy for pre-eclampsia.
11	35	40	34	35	
12	63	40	51	20	Unco-operative.
13	68	40	54	14	Pneumonia, at home.
14	62	24	24	14	Hotel meals.
15	23	40	58	26	Unco-operative.
16	54	26	16	11	Hiatus hernia; hotel meals.
17	70	35	20	10	Hypertensive.
18	30	23	24	18	
19	19	40	42	20	
20	37	40	24	25	Awaiting mammaplasty.
21	30	40	30	30	Alcoholic.*
22	50	40	40	27	
23	64	30	22	23	
24	63	40	40	17	Myxoedema; reduced thyroid dosage.
25	60	40	34	17	Grossly osteo-arthritic knees.
26	50	40	45	28	Abdominal lipectomy.
27	22	40	45	26	
28	46	40	40	22	
29	50	40	56	35	*
30	26	40	14	18	*
31	20	40	28	19	Mammaplasty.*
32	62	14	14	11	*
33	39	40	24	17	Irregular dieting; alcoholic.
34	23	40	35	26	
35	63	40	45	24	Hotel meals.
36	41	40	42	30	
37	22	40	54	21	Irregular dieting.
38	26	27	28	14	
39	54	25	15	14	Awaiting lipectomy.*
40	48	40	24	14	Irregular dieting; depressed.
41	15	40	45	30	
42	46	25	22	20	*
43	46	26	50	24	

TABLE 1—Continued

Patients		Consecutive Days of Treatment	Overweight (lbs.)	Weight Loss (lbs.)	Remarks
Case No.	Age (yrs.)				
			Males		
44	54	40	45	32	Duodenal ulcer; died postoperatively.
45	54	20	12	12	Plastic repair of ptosed eyelid.*
46	37	20	45	13	
47	50	40	98	30	
48	40	40	38	37	Hiatus hernia.
49	34	25	36	22	
50	60	40	56	40	Polyp of colon removed.*
51	53	40	40	30	Gout.
52	45	40	40	20	Cardiac neurosis.
53	50	25	20	17	
54	62	40	60	42	Cardiac ischaemia.
55	49	40	35	19	Grossly irregular dieting; alcoholic.
56	39	28	60	18	
57	52	40	52	28	
58	38	40	27	25	
59	30	22	18	15	
60	35	17	54	17	
61	53	40	26	24	
62	32	40	28	20	Irregular dieting.
63	32	40	38	31	

* See Table 2 and text.

the first time. None of them had any difficulty in coping with their normal activities. The symptoms commonly associated with obesity, such as lassitude, breathlessness on exertion, "rheumatic" aches and pains, and headaches, all subsided a few days after the treatment began.

From the surgical point of view it was important that the skin should not sag or become flaccid despite the rapid loss of from 25 to 40 pounds. Loss of subcutaneous fat—a result so common with other methods of reducing—did not occur. After operation the skin always healed by first intention; and this was particularly important and gratifying after reduction mammaplasty and abdominal lipectomy. Acute appendicitis developed in 2 patients during treatment, which was continued throughout their stay in the hospital. There was no difficulty in inducing or maintaining anesthesia, and after an uneventful postoperative recovery both were discharged from the hospital within ten days. Three other patients underwent operations during the course of therapy (Cases 2, 43 and 45; Table 2). None experienced any ill effects and therapy was continued immediately after the operation.

Of the 9 patients who underwent operations after treatment, 3 had mammary reductions, 1 a mammary reconstruction, and 1 an abdominal lipectomy. None of those patients gave any cause for anxiety. Table 2 shows details of the operations on the others, 1 of whom died. Patient 44, a man aged 54 with a 20-year

TABLE 2

Surgical Cases

Case No.	Remarks
	a) Surgery before treatment
32	Mammary hypertrophy; plastic reduction.
42	Dislocated hemi-pelvis with fractured neck of femur.
	b) Surgery during treatment
2	Mammary hypertrophy; hiatus hernia; plastic reduction.
30	Acute appendix and ovarian cyst removed; back at work in two weeks.
43	Diagnostic curettage.
45	Repair of ptosed upper lid; hospitalized for two days.
31	Acute appendix; hospitalized for ten days.
	c) Surgery after treatment
3	Mammary hypertrophy; plastic reduction.
9	Mammary augmentation following bilateral excisions for fibro-adenosis.
26	Abdominal lipectomy; excision of olecranon spur and bursa.
29	Diagnostic curettage and cautery of cervix; hospitalized for two days.
30	Unilateral breast reconstruction following traumatic amputation.
31	Mammary hypertrophy; plastic reduction; hospitalized for ten days.
40	Rhinoplasty.
44	Duodenal ulcer; died postoperatively. (See Discussion.)
50	Polyp of colon removed by diathermy; general anaesthetic; hospitalized for ten days.
	d) Awaiting surgery.
20	Ptosed hypertrophied breasts.
39	Abdominal lipectomy.

history of duodenal ulcer, lost 32 pounds during treatment, being free of pain throughout. He was referred for surgery on account of the lengthy history and the size of the ulcer. He died on the eighth day after operation from the effects of a burst duodenal stump which was demonstrated at necropsy.

Two patients were treated after an operation. The first was a woman aged 46 (Case 42) who had been confined to bed for twelve weeks following a dislocated hemi-pelvis and a pertrochanteric fracture of the neck of the femur. Her muscles had become quite flabby and she had gained over a stone in weight: after a short course of treatment she lost 20 pounds, had a full, painless range of hip movement, and was fully ambulant. She was back at work before the completion of her course. The second patient (Case 32) presented nine months after a reduction mammaplasty, with which she had been most gratified. She had gained weight and was worried that it might spoil the results of the operation, but she quickly lost 11 pounds and her weight was restored to the previous level.

Two other patients are awaiting operation (Table 2). The many advantages of

preoperative weight loss without ill effect are likely to be appreciated by surgeon and patient alike.

Three patients (Cases 2, 16 and 48) with radiologically demonstrable diaphragmatic hernia causing fairly severe symptoms were all trouble-free within a few days of starting treatment and remained so throughout the course. They were discharged without further treatment.

CONCLUSIONS

The technique, as described by Simeons and illustrated by the present series, is a satisfactory and safe method of reducing overweight patients without hardship. It offers many advantages for planned abdominal and plastic surgery, being rapid, effective and without adverse effects during anesthesia, operation, or the postoperative or convalescent period. A number of patients who would otherwise be unfit for operation or, at best, a bad risk, may be rendered "safe." Patients who have been treated preoperatively will avoid the cardiovascular and respiratory embarrassments of the obese.

SUMMARY

Sixty-three overweight patients were treated with chorionic gonadotropin and a low calorie diet to assess the suitability of the method as an adjunct to planned surgery. The satisfactory results show that the technique can produce effective, rapid and safe weight reduction. Patients who required an emergency operation during the treatment did extremely well.

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CHLORDIAZEPOXIDE AS A BROAD-SPECTRUM PSYCHOSEDATIVE

IRA N. ROSENSTEIN, M.D.* AND CHARLES W. SILVERBLATT, M.D.†

Miami, and Coral Gables, Florida

Cardiovascular disease—whether of coronary, rheumatic or hypertensive etiology—debilitating pulmonary disease, gastro-intestinal disorders, acute or chronic alcoholism and carcinoma frequently require adjunctive tranquilizing therapy in addition to the specific medication or therapeutic procedure for treatment of the primary condition. The need for allaying fear, apprehension and anxiety in the acutely ill patient with myocardial infarction is of prime importance. The relationship of stress and anxiety to coronary artery disease is receiving widespread attention, and present data point to the necessity for decreasing stress in the pre-coronary patient. The vexatious problem of insomnia is becoming increasingly prominent among post-myocardial infarction patients. The emotional overlay involved in many gastro-intestinal disorders is also an important factor, as is the syndrome of agitation, tremulousness, anorexia and behavioral difficulties characteristic of chronic alcoholism.

As an aid to specific therapy in this wide range of medical problems, tranquilizers have been extensively employed. However, the well documented side-effects associated with rauwolfia (1, 2) and phenothiazine compounds (3, 4) as well as with meprobamate have stimulated continued research for a less toxic ataractic agent. A recent development in this area has been the synthesis of an entirely new compound, chlordiazepoxide.[1] Chemically unrelated to any of the foregoing compounds, chlordiazepoxide is 7-chloro-2-methylamino-5-phenyl-3H-1,4 benzodiazepine 4-oxide hydrochloride. It possesses 3 basic pharmacologic actions which have been demonstrated both in extensive experiments with animals (5) and in subsequent clinical studies. These actions are: *a*) sedative, tranquilizer and muscle relaxant (6–8); *b*) appetite stimulator (9); and *c*) anticonvulsant (10, 11).

This study was undertaken to evaluate the usefulness of chlordiazepoxide in both hospital and clinic cases of organically based disorders, the treatment of which might be enhanced by suitable adjunctive medication designed to relax and calm the patient.

The difficulties inherent in the evaluation of a new drug, with all the nuances of activity and uncertainty of dosage, are fully recognized. Added to this is the problem of appraising a tranquilizer in terms of factors such as "nervousness," "apprehension" or "anxiety"—symptoms which have thus far defied precise measurement. There is no single test or series of laboratory determinations that will indicate, except in a rather gross manner, the degree of nervousness or apprehension that exists in a given subject.

* *Address:* The Physicians' Group, 1431 North Bayshore Drive, Miami 36, Florida.

† Assistant Chief, Department of Medicine, VA Hospital, Coral Gables, Florida.

[1] Librium; Hoffmann-La Roche, Inc., Nutley, New Jersey.

These symptoms are largely subjective, expressed by the patients as, "I am very nervous," and only partly recognized by the examiner through the patient's speech content, facial expression, mannerisms and general demeanor. Further compounding these difficulties is the fact that many who are in need of tranquilization are highly susceptible to suggestion, so that often initial improvement with new therapy represents a placebo effect.

On the other hand, certain physical signs are susceptible to objective measurement. For example, loss of weight or inability to gain weight may point to a severe mental disturbance, and an excessive gain in weight resulting from compulsive eating may signify some type of neurosis. Sighing respirations and tremors alert the clinician to look for an underlying psychiatric problem. However, since these manifestations may be signs also of organic damage, caution must be exercised in classifying them as "psychogenic."

Bearing these problems in mind, we undertook to evaluate chlordiazepoxide in a series of patients with a variety of organic disorders.

METHODS AND MATERIALS

The effect of chlordiazepoxide was studied in 125 patients at the Veterans Administration Hospital, Coral Gables, Florida. Seventy-five were seen on the Medical Service Wards and 50 in the Regional Office Out-patient Division. The in-patient group was cared for in open wards of the Medical Service, rather than in closed wards of a psychiatric service reserved for severely deranged persons. They represented to some extent the type of patient seen by general practitioners and internists.

The clinical categories among the hospitalized patients included acute alcoholism with and without cirrhosis, gastro-intestinal disease, acute myocardial infarction accompanied by anxiety, hypertensive cardiovascular disease, pulmonary disease, carcinoma, and psychoneurosis with a component of anxiety (Table 1). The out-patients fell into somewhat similar disease categories, but the severity of their diseases did not currently require their hospitalization.

The patients were drawn at random on the basis of their need for sedation, muscle relaxation, appetite stimulation or anticonvulsant therapy. [Our use of the drug in anticonvulsant therapy has been described in previous papers (10, 11)].

Before initiating treatment with chlordiazepoxide, laboratory determinations included urinalysis, peripheral blood count (red cells, white cells, differential count and platelets) hemoglobin, hematocrit, the levels of blood urea nitrogen (BUN), serum sodium, potassium, chloride and bicarbonate, bromsulfalein retention, and an electrocardiogram. After initiating therapy, these studies were repeated on an average of every two weeks. Blood pressure (with the patient recumbent, then standing) and pulse rate were recorded two hours after each dose of the drug. In addition, gastric analyses (fasting) were performed in 5 cases.

Except for a few patients who were not aware that a new drug was being used, all were told that a new medication was being employed which had proved of value in others with their problems. They were forewarned about possible ataxia.

TABLE 1

Results with Chlordiazepoxide in 75 In-Patients

	Therapeutic Responses (Category A, B or C) in						
Acute alcoholism with or without cirrhosis	Gastro-intest. disease	Acute myocard. infarction with anxiety	Post-myocard. infarction complications	Hypertensive cardiovasc. disease with agitation	Pulmonary disease	Psychoneurosis, anxiety, miscellaneous	Carcinoma
A-1*	A-3	A-4*	A-5	A-23 (OP)**	A-38, 39	A-7, 10, 11	A-6*
A-2	A-13	A-12, 31	A-15, 16 (OP)**	A-40	A-43, 44	A-14, 24 (OP)**	A-8, 32
A-9, 25, 26, 27	B-2	A-41	A-17, 18 (OP)**	B-1*	A-45, 47	A-29, 34, 36	A-42
A-30, 33, 35, 37	C-10		A-19, 20 (OP)**	B-6 (OP)**	B-16	B-3, 5, 7, 11	B-12, 14
A-46			A-21, 22 (OP)**	B-8	C-11, 12	C-3, 4, 5	B-15
B-4, 10			A-28	C-6, 7 (OP)**		C-8, 9	C-1*
			B-9, 13				C-2
Total 13	4	4	12	7	9	17	9

Total therapeutic responses:

Category A : 47 = 62.7%
Category B : 16 = 21.3%
} 84% partial to complete relief of symptoms.
Category C : 12 = 16.0%

No. of cases = 75 100.0%

* Case history cited. The numeral refers to the Case number.

** These patients had been hospitalized, but at the time of initiation of chlordiazepoxide therapy they were treated on an out-patient basis.

The initial dose was 25 mg. three times daily. It was decreased to 25 mg. twice daily in some instances, increased in others to 50 mg. three times daily (on a highly individualized basis), and in alcoholics and acutely agitated patients increased up to 100 mg., twice or three times daily. This individual adjustment of dosage is illustrated in the case histories.

The patients were discouraged from volunteering information they thought the examiner might want to hear. In repeated follow-ups at the bedside or in the clinic, the patients were asked: "Do you notice any improvement, lack of change, or worsening in your 1) sleeping hours, 2) degree of excitability or agitation while awake, 3) appetite"? Thus, the line of questioning tended to discourage the patient from supplying glowing reports; in addition it tended to keep the physician always on the alert for undesirable side-effects. Throughout, the attempt was made to avoid what Koteen (12) has described as "tranquilization of the physician" along with the patient.

CATEGORIES AND TABULATION OF RESULTS

The therapeutic results were classified according to the degree of remission of symptoms for which the medication was administered (Tables 1 and 2). Patients falling into Category A experienced complete or virtually complete relief of symptoms and signs noted prior to therapy. Category B represented the patients

TABLE 2

Results with Chlordiazepoxide in 50 Out-Patients

Therapeutic Responses (Category A, B or C) in					
Cor. art. disease, angina; previous infarction	Rheumatic heart disease with severe anxiety	Hypertensive cardiovasc. disease	Gastro-intestinal disease	Psychoneurosis, anxiety, miscellaneous	Carcinoma
A-3	A-20	A-28, 35	A-13	A-1, 2, 4, 6, 7, 10, 18, 19	A-45
A-5*	A-37	A-48, 49	A-16	A-21	A-50
A-8, 9					
A-12, 22, 39		B-15*	B-41	A-23, 24, 25, 26, 27, 30, 31, 32	A-34
A-44, 47			C-14*		
B-11*				A-40, 42, 43, 46	
B-29				B-17, 33	
Total 11	2	5	4	25	3
22%	4%	10%	8%	50%	6%

Total therapeutic responses

Category A : 43 = 86%
Category B : 6 = 12%
Category C : 1 = 2%

98% partial to complete relief of symptoms.

No. of cases = 50 100%

* Case history cited. The numeral refers to the Case number.

TABLE 3

Summary of Results with Chlordiazepoxide in 125 Patients

Category of Therapeutic Response	In-Patients		Out-Patients		Combined	
	No. of cases	% total	No. of cases	% total	No. of cases	%
A	47	62.7%	43	86%	90	72%
B	16	21.3%	6	12%	22	17.6%
C	12	16.0%	1	2%	13	10.4%
Total No. of cases	75		50		125	

who exhibited partial relief of symptoms, and Category C included those who showed no improvement or whose clinical state became worse while receiving chlordiazepoxide therapy.

For detailed descriptions of the manner by which the activity of chlordiazepoxide was manifest, typical case histories are reported under each of the three therapeutic categories. The percentage indications of effectiveness in the in-patient and out-patient groups are shown in Tables 1 and 2 and summarized in Table 3.

CASE HISTORIES (IN-PATIENTS)

Category A. Therapeutic Success

Case 1. *A. J.*, a 33-year-old male, had undergone a subtotal gastrectomy seven years prior to admission, and had been hospitalized seven months before the current admission for treatment of infectious mononucleosis. He was known to suffer from severe alcoholism and on admission presented slight hematemesis secondary to alcoholic gastritis. In addition, he had impending delirium tremens with gross tremors, hyperesthesia and marked restlessness. It was well substantiated that the patient had scarcely slept for a week prior to the current admission nor had he had a substantial meal in several months.

During the first twenty-four hours the patient received promazine, 75 mg. intramuscularly every three hours, with little effect. This was discontinued and chlordiazepoxide was started, 50 mg. three times daily. Within twenty-four hours he was less restless, with lessening of his tremors and had begun to eat. By the third day he was sleeping well at night. The results of liver tests were essentially normal, and his appetite was excellent. By the fifth day of therapy the patient was eating ravenously, requiring night feedings. He gained 6 pounds without apparent edema. One week later, the total weight gain was 7 pounds and the finger and hand tremors were markedly reduced. The patient was fully alert, had a voracious appetite, and volunteered the information that he had "never slept better at night without interruption" since using the new medication.

The following day the dosage was decreased to 50 mg. twice a day, and twenty-four hours later it was further decreased to 25 mg. twice a day. On the twenty-first day of therapy the patient was discharged. His total weight gain was 11 pounds. There were no tremors, and he was sleeping well. No abnormalities of gastric, liver or renal function, or of the blood count developed during therapy.

Case 4. *V. A.*, a 40-year-old male, had a history of coronary atherosclerosis of four years' duration, involving a previous myocardial infarction (well documented) and numerous anginal attacks thereafter. He had had multiple previous admissions for angina and always exhibited an almost morbid preoccupation with his cardiac status. The current admission

was similarly prompted by chest pain, and this time serial electrocardiograms showed an acute lateral-wall myocardial infarction. Three days after admission the chest pain had become infrequent, but the patient described pain and numbness in the left shoulder and hand—unrelieved by frequent salicylates, codeine and meperidine and only partially relieved by morphine sulfate. All studies failed to show further infarction. Chlordiazepoxide was subsequently begun in a dosage of 25 mg. every eight hours, and within three days the pain and anxiety had disappeared. His previous four years of alarming concern for his condition was no longer present and he began making plans to return to school to study radio communications. The total duration of therapy was twenty-five days, and no abnormalities were noted in the laboratory findings.

Case 6. P. M. was a 62-year-old male with arteriosclerotic heart disease, chronic congestive heart failure, bilateral cataracts, and infiltrating squamous-cell carcinoma (Class III) of the esophagus (determined by biopsy one year previously). Despite generalized edema, pitting edema (3-plus) to the mid-thigh and moderate ascites, his weight was only 85 pounds. He was very "nervous" and anorectic but not dysphagic, and described multiple nonspecific abdominal pains. He was virtually bedridden. Because of marked anorexia, he required several hours merely to drink a few ounces of milk. The electrocardiogram showed left ventricular hypertrophy and first-degree heart block. Urinalysis findings were unremarkable, the blood urea nitrogen level was 29 mg. per 100 ml., and the hematocrit was 35 per cent immediately before chloridazepoxide was administered. The patient's course was as follows:

Day 1: Discontinuation of long-standing medications — methadone (25 mg.) and promethazine (15 mg) both given intramuscularly every three hours; phenobarbital (100 mg. four times daily); and routine whiskey and egg nog—and initiation of chlordiazepoxide therapy (50 mg. three times daily).

Day 2: The patient was very shaky, "nervous" and crying frequently, seemingly from rapid and complete withdrawal of the multiple narcotics and sedatives. The following day he was very lethargic.

Day 9: "Nervousness" decreased markedly. Appetite was greatly improved and the patient was eating three meals a day. The peripheral pitting edema was now only 1-plus. The ascites was also greatly decreased.

Day 19: He was walking the length of the corridor. The hemogram, serum electrolyte levels and bromsulphalein retention remained normal.

Day 35: Improvement was such that arrangements for transfer to a nursing home were initiated, with provisions for continuing chlordiazepoxide therapy on an out-patient basis.

Day 46: Sudden development of fever to 103°F., with pyuria, confusion and lethargy related to both a flare-up of a genito-urinary infection and bilateral bronchopneumonia, the latter confirmed radiographically. Within ten days the infections had cleared with antibiotic therapy (given on the basis of culture and sensitivity determinations) and the patient was afebrile.

Day 75: He was discharged to a nursing home. Three months later he was still doing well. The congestive heart failure was well controlled and there had been a further weight gain to 97 pounds.

Cases 15–22 (OP).[2] These 8 male patients, including 2 physicians (average age, 54 years), each had sustained at least one myocardial infarction within the previous one or two years, and each was suffering from intermittent diurnal anxiety and persistent insomnia. Angina was mild or absent in the majority. There was no evidence that the insomnia was due to occult congestive heart failure, except in 1 patient; he was digitalized and the insomnia disappeared. All 8 had been receiving numerous tranquilizers with little or no relief, and in several instances the daily intake of multiple tranquilizers was astonishingly high. While receiving chlordiazepoxide, this group was treated strictly on an out-patient basis, the average dosage being 25 mg. every twelve hours plus a 25-mg. bedtime supplement. All

[2] These patients had been hospitalized but at the time of initiation of chlordiazepoxide therapy, they were treated on an out-patient basis.

responded rapidly (within one to three days) and broke their long-standing pattern of anxiety, apprehension and insomnia which had developed and progressed nightly with the setting of the sun.

Category B. Partial Therapeutic Success

Case 1. *C. S. A.*, a 60-year-old male, had a long-standing history of severe diastolic hypertension and renal difficulties previously described as chronic pyelonephritis. Various renal function studies early in 1959 demonstrated a nonfunctioning left kidney and persistent azotemia with a BUN level varying from 50 to 70 mg. per 100 ml. The patient underwent a left nephrectomy and sympathectomy, but the diastolic hypertension persisted postoperatively. Reserpine, hydralazine and chlorothiazide were then started, with good results. The patient, however, was very unreliable and cantankerous; he discontinued these drugs shortly after discharge, so that he soon required readmission. The diastolic blood pressure and the BUN level had risen, and paroxysmal atrial fibrillation was present in association with congestive failure. The patient was digitalized, and the hypertension and paroxysmal fibrillation improved. However, the BUN level continued to fluctuate, and his appetite was very poor. He remained a serious personality problem, often refusing medications, persisting in smoking in bed despite frequent reminders to the contrary, and being very demanding and insulting to the medical staff. On one occasion he hurled an intravenous infusion bottle across the room.

Numerous tranquilizers had been tried without success. Finally, chlordiazepoxide was started in a dosage of 25 mg. every eight hours. Within seventy-two hours the patient was remarkably docile, but he became so listless and lethargic that he was often too weak to feed himself. On the ninth day of therapy the dosage was decreased to 25 mg. every twelve hours. During the next week he became less lethargic, but was still weak. The BUN level was rising and it was difficult to determine how much of the drug he was excreting. Therefore his medications were cut to a minimum and finally discontinued. Again he became a difficult management problem in terms of his personality. Cachexia persisted, with varying degrees of azotemia. Several weeks later the patient died.

Category C. Therapeutic Failure

Case 1. *M. N.*, a 38-year-old female, was admitted with carcinoma of the breast with lung metastases. She was receiving very high doses of numerous narcotics, and chlordiazepoxide was introduced in an attempt to: 1) decrease the frequency of narcotic medication for pain secondary to nerve invasion, and 2) produce euphoria. However, the pain continued to be extremely severe and the drug failed on both counts, even in doses of 100 mg. three times a day. The patient was pre-terminal and the drug was, therefore, discontinued after several days of therapy because of the great personal discomfort to the patient during this brief weaning period.

CASE HISTORIES (OUT-PATIENTS)

Category A. Therapeutic Success

Case 5. A 45-year-old retired colonel with previous myocardial infarction and severe angina required unusually large amounts of sublingual nitroglycerine tablets for relief. His pain was so frequent and severe that he was willing to undergo a surgical operation (Beck I procedure) for attempted relief of angina. In the interim, chlordiazepoxide therapy was started in a dosage of 10 mg. three times daily. The frequency and severity of his anginal episodes were so greatly reduced that he refused surgery. The duration of therapy (same dosage) to date has been four months, and relief from angina continues.

Category B. Partial Therapeutic Success

Case 15. A 53-year-old male with arteriosclerotic and hypertensive cardiovascular disease had a previous cerebrovascular accident with residual left hemiparesis. For the past

five months he has been receiving 10 mg. of chlordiazepoxide three times daily. There has been a moderate decrease in anxiety, fluctuations of blood pressure and insomnia.

Category C. Therapeutic Failure

Case 14. A 64-year-old male with severe psychoneurosis and anorexia was given chlordiazepoxide in a dosage of 10 mg. twice daily for two months, without any change in his clinical status. The dosage was not increased because the patient did not return for further study.

GENERAL FINDINGS

Among the 75 in-patients, 47 were in Category A, 16 in Category B and 12 in Category C. Among the 50 out-patients, 43 were in Category A, 6 in Category B and 1 in Category C.

The striking effects observed with chlordiazepoxide were initial tranquilization, and stimulation of the appetite occurring concomitantly or after tranquilization had been achieved. The most notable successes were obtained in the cases of acute alcoholism with impending or frank delirum tremens, and in cases of myocardial infarction (both in the acute and recovery phases) in which anxiety and insomnia were the most troublesome symptoms.

The onset of effective drug action (oral route) was noted within two to six hours. The duration of activity after discontinuance of the drug was usually between thirty-six and forty-eight hours.

The laboratory findings showed no abnormalities of the blood count, urine, blood urea nitrogen and serum electrolytes levels, or the electrocardiogram attributable to administration of the drug. Indeed, in many patients with initial liver function abnormalities there was a more rapid return toward normal (when physiologically possible) as tranquilization was achieved and appetite improved.

The major side-effects were grogginess and ataxia, only partly dose-related. Thus some patients receiving 25 mg. twice daily experienced more marked lethargy and drowsiness than alcoholics receiving 100 mg. two or three times daily (the increased drug tolerance being especially prominent in patients with acute alcoholism). In some cases, even without adjustment of dosage, the mild ataxia which developed occasionally would subside within two to four days without loss of therapeutic effect. In only 1 case was there significant postural hypotension as judged solely by the blood pressure reading; there were no clinical symptoms.

In patients with organically based pain as a prominent symptom (herpes zoster or terminal carcinoma), chlordiazepoxide appeared to be of little value. However, even in these cases, when it was used concomitantly with narcotics it still exerted its appetite-stimulating effect.

DISCUSSION

Chlordiazepoxide exerted a dual action of tranquilization and appetite stimulation. Admittedly, "1-plus" to "4-plus" nervousness, or "mild" and "moderate" agitation may mean different things to different observers. However, what appeared to be of prime importance in this study was not the specific "degree"

of nervousness or agitation, but the over-all changes and the direction of these changes.

Chlordiazepoxide was notably of value in patients with coronary disease and myocardial infarction who were troubled with apprehension and anxiety in the daytime and insomnia at night.

Also striking was the tranquilizing effect in acute alcoholism. In these cases the characteristic agitation, jitteriness and anorexia were promptly alleviated.

Further studies are required in patients with severe pulmonary insufficiency to determine the proper place of the drug in their therapeutic regimen.

Chlordiazepoxide appears to be effective over a wide dosage range; therefore, generalizations concerning optimal dosage are difficult. However, a dosage of 0.5 to 1.0 mg. per Kg. of body weight is suggested as a workable basis for further adjustment.

The following are 3 tentative recommendations: *1*) In the mildly agitated patient in whom stimulation of appetite is also desirable, the smallest dose capable of producing tranquilization should be used. Thus, smaller and more frequent doses (10 to 25 mg. three times daily) are preferred to larger and less frequent doses (50 mg. twice daily). *2*) In acutely and severely agitated patients (*e.g.*, acute alcoholics), dosages as high as 100 mg. twice or three times daily appear to be both effective and safe. Once the initial pronounced tranquilizing effect has been achieved, smaller dosages should be used to overcome the marked lethargy while maintaining the appetite-stimulating action. Patients who appear "snowed under" are generally easily roused for feedings. *3*) In frankly depressed patients without agitation, when stimulation of the appetite is the sole purpose for using the drug, the initial dosage should not be more than 25 mg. daily. If stimulation of the appetite cannot be achieved with 25 mg. two or three times daily, it is unwise to increase the dose, for more profound depression may result in further decreasing the ingestion of food.

A striking characteristic of the drug is the absence of irreversible laboratory or clinical side-effects. Lethargy, drowsiness and ataxia—the symptoms which occur most consistently—can be readily reversed by suitable adjustment of the dosage.

Chlordiazepoxide should not be used when the level of consciousness must be repeatedly assessed; nor should it be employed in the treatment of patients with renal disease and inadequate or unpredictable urinary excretion.

SUMMARY

Chlordiazepoxide, a new chemical agent unrelated to any other psychotropic drug, was evaluated in 125 patients with a variety of organically based disorders involving the cardiovascular, gastro-intestinal and pulmonary systems, and with chronic or acute alcoholism. Seventy-five, who were severely ill, were treated on the Medical Service wards, and 50 were treated as out-patients—all at the Coral Gables (Florida) Veterans Administration Hospital.

Patients were selected on the basis of need for tranquilization, appetite-stimulation and nocturnal sedation. In all instances, there was a prominent component

of anxiety, apprehension and agitation as a complicating symptom of the primary disorder.

Of the 75 hospitalized patients, 84 per cent obtained either complete or partial relief of their anxiety, insomnia and anorexia during chlordiazepoxide therapy. Of the 50 ambulatory patients, all but 1 responded favorably to the drug.

The most notable therapeutic successes were achieved in the treatment of coronary atherosclerosis with angina pectoris and/or myocardial infarction, and of acute and chronic alcoholism.

The drug was of little value when severe pain was a prominent organically based symptom in carcinomatous patients.

The only side-effects were grogginess and ataxia which were relieved by adjustment of the dosage.

The range of dosage effectiveness proved to be so broad that optimal schedules await further definitive study.

The drug is contraindicated for analgesia in carcinoma and in renal disease, or whenever the level of consciousness needs to be repeatedly assessed.

Chlordiazepoxide appears to have a wide range of usefulness for calming patients whose organic disorders are accompanied by anxiety and agitation.

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Abstracts of Current Literature

ISOSORBIDE DINITRATE IN TREATMENT OF ANGINA PECTORIS. PRELIMINARY CLINICAL IMPRESSION.

Albert, A. *Journal-Lancet* **81:** 112 (March) 1961.

Isosorbide dinitrate in a usual dose of 10 mg. four times daily was given to 28 patients with coronary insufficiency associated with angina pectoris. Their ages ranged from 46 to 83 years, and averaged 66 years. Twenty-four patients responded favorably with a 77 per cent decrease in the number of attacks of angina pectoris. Four patients had complete relief of symptoms. The benefited patients experienced an increase in activity tolerance and had an increased sense of well being. When a placebo was instituted in 4 patients, their original symptoms rapidly returned but disappeared again when isosorbide dinitrate therapy was reinstituted. One patient had a fair response, and 1 patient a poor response. Three patients discontinued the substance because of extreme vascular headaches. Such headaches occurred in 2 other patients who continued treatment; subsequently, one patient became able to tolerate 5 mg. four times daily with a good response. In this study, the benefits from isosorbide dinitrate appeared to be more marked with continued use. The drug appeared to exert a more consistent and profound effect than any drug previously used in the prophylaxis of angina pectoris.

BENIGN AND MALIGNANT CUTANEOUS TUMORS IN THE ELDERLY

Becker, S. W., and Brennan, B. B. *Arch. Dermatol.* **83:** 262 (Feb.) 1961.

When the relative frequency is calculated by dividing the percentage of tumors in each age group by the percentage of the population in that group, the incidence of benign and malignant tumors of the skin in elderly people becomes greater than age-incidence charts indicate. The three most common *benign neoplasms* in older people are seborrheic keratosis, acquired hemangioma, and pigmented nevus. Seborrheic keratosis is composed predominantly of basal type cells and is only of cosmetic importance. Acquired hemangioma is commonly seen on the trunks of elderly persons. Treatment, if desired, consists of cryotherapy, electrocautery, or fulguration. Biopsy should be performed to exclude melanoma before excising pigmented nevi. The most important *malignant epithelial tumor* is prickle-cell carcinoma. Its incidence rises with age and it accounts for the highest mortality rate from cutaneous carcinoma. This lesion appears primarily upon exposed areas as flesh colored papules or nodules which extend laterally and may ulcerate. It may arise on the palms, soles, mucocutaneous junctions, and mucosae. The majority of surface lesions occur in men. The lesion most frequently diagnosed among cutaneous malignancies is actinic keratosis. Nonelevated actinic keratoses may be treated by cryotherapy, electrocautery, or fulguration. Prickle-cell carcinoma develops in about 20 per cent of such lesions. Elevated lesions always require a biopsy. The next most frequent diagnosis is basal-cell carcinoma which is only locally malignant and does not metastasize. A pearly, rolled, translucent border which is easily curetted out is characteristic. The lesions may ulcerate, become elevated, or change color to gray, brown, or black. *Therapy* for cancer of the skin consists of destruction or removal. When surgical removal is not possible, irradiation is the treatment of choice. Adequate biopsy is a necessity. Care must be taken to make removal adequate and irradiation sufficiently extensive. Frequent observation is necessary in order to detect any recurrence in its early state. The majority of cutaneous carcinomas can be cured if treated early and adequately. Evidence is against slow spread and decreased metastasis in the aged. In prickle-cell carcinoma, the size, grade, duration, location, and degree of anaplasia are guides to regional lymph node dissection. The size of the tumor is probably the primary factor influencing prognosis. *Melanoma* occurs more frequently in elderly people than has been appreciated. Its importance is secondary to prickle-cell carcinoma. A slight

decrease in relative frequency is seen in the oldest age groups. Early diagnosis and radical therapy, when feasible, may improve the prognosis.

ULCERATIVE COLITIS IN THE AGED.

Bercovitz, Z. T. *Am. J. Gastroenterol.* **35:** 213 (March) 1961.

Ulcerative colitis is likely to occur in the aged without premonitory symptoms. It may progress so rapidly as to become a surgical emergency within the first year, or cause death. The mode of onset varies; there may be obstruction of the colon at the level of the sigmoid, an acutely toxic megacolon with signs of the fulminating form of the disease, perforation or evidence of impending perforation, massive hemorrhage, and most often watery diarrhea. The first evidence of the disease may be located in the rectum and sigmoid or involve a small segment of adjoining distal descending colon. The chronic forms of the disease may have been present for ten to thirty years. At first, there will have been ulcerations and changes in the mucosal pattern. Later these will have disappeared and roentgenograms will show evidence of stricture and narrowing and alternating areas of dilatation and spasm. Conditions that must be considered in the differential diagnosis include malignancy of the colon, diverticulosis, diverticulitis, carcinoid tumors, staphylococcus enterocolitis, and dysentery. Terminal ileitis may be associated with ulcerative colitis. The causes of bleeding such as polyposis, duodenal or gastric ulcer, gastric carcinoma, esophageal varices, telangiectasis, and mesenteric thrombosis must be given careful consideration. The most serious problems are presented by complicating conditions due to age itself, such as diabetes, arteriosclerotic heart disease, hypertension, arteriosclerosis, cardiovascular renal complications, and chronic liver disease. Prognosis is related directly to the age at onset of the disease. Patients past the age of 70 years at the onset are unlikely to survive the first year. During the 50's, patients usually survive under medical management and few require surgery. Treatment depends upon the stage and severity of the colitis and the complicating factors. Emergency treatment such as whole blood transfusions, intravenous fluids, and electrolyte and protein replacement, will be required in the case of severe diarrhea, hemorrhage, megacolon with the acute fulminating forms of the disease, complete physiologic systemic degeneration, and collapse related to adrenocortical failure. Chloramphenicol is the antibiotic of choice in the emergency treatment and is used in dosages of 1 to 2 Gm. per day intravenously or intramuscularly. Adrenal corticosteroids should be used only under the most serious conditions and with caution. They must not be given in the presence of an acutely toxic megacolon with impending perforation. Adrenocortical steroid support must be given during surgery and postoperatively. During the emergency phase of ulcerative colitis, powerful sedatives and especially phenobarbital are to be avoided. Intravenous or intramuscular Benadryl and Dramamine are beneficial, and meprobamate is well tolerated. Anticholinergic agents reduce small bowel spasm and motility. For renal sphincter control, a serious and troublesome problem, intra-rectal instillation of meticortalone acetate relieves symptoms. For acute and subacute exacerbations of ulcerative colitis, small stimulating doses of ACTH and prednisone are indicated, with a reduction to maintenance levels when possible. Antibiotic and antibacterial agents used during acute exacerbations and as maintenance dosages include chloramphenicol, carbarsone, diodoquin, and erythromycin in rotation or in combination. Narcotics are contraindicated except in rare cases with uncontrollable pain. Diet is an important phase of treatment and eating should be encouraged. Alcohol, coffee, and highly spiced foods are prohibited. Surgical treatment is called for in the presence of massive or repeated uncontrollable hemorrhage, a progressive downhill course despite therapy, intestinal obstruction, a change from a mild to a fulminating form of the disease with megacolon and evidence of impending perforation, and carcinoma. The older the patient, the more likely he is to become a surgical emergency. Hypothermia as an adjunct to anesthesia is valuable in reducing shock and allows a more rapid and precise surgical technic. Postoperative care requires especially careful watch for derangements in the levels of calcium, proteins, electrolytes,

hemoglobin, hematocrit, and blood pressure. Between the second and seventh days, there is great danger of abrupt peripheral vascular collapse. The treatment is intravenous hydrocortisone, and some patients may require small maintenance dosages of adrenocortical steroids for some time postoperatively. The operation usually performed is total colectomy with ileostomy, after which a plastic ileostomy bag is applied.

ÜBER DIE LOKALISATIONEN DES KEHLKOPF- UND HYPOPHARYNXKARZINOMS IN BEZUG AUF DAS LEBELSALTER (LOCALIZATION OF CANCER OF LARYNX AND HYPOPHARYNX ACCORDING TO AGE.)

Filippi, P., and Caligaris, F. *Laryng. Rhinol.* **38:** 818, 1959; through Excerpta med. (Gerontol. & Geriatrics) **4:** 141, 1961.

A statistical analysis of 829 cases of carcinoma of the larynx and hypopharynx showed the peak incidence of the primary lesion at different sites to vary in different age groups. The epiglottic, vestibular, and ventricular carcinomas arise earlier than those of the aryepiglottic folds, vocal cords, pyriform fossa and glossoepiglottic region. The different distribution of cancer localization in various age groups is statistically significant. The incidence seems to differ according to the dominant influence of either exogenous or endogenous carcinogenic factors on different regions of the larynx and hypopharynx.

ANTICOAGULANT THERAPY IN CEREBRAL THROMBOSIS AND CEREBRAL EMBOLISM. A NATIONAL COOPERATIVE STUDY, INTERIM REPORT.

Fisher, C. M. *Neurology* **11:** 119 (Apr.) 1961.

This report is made eighteen months after the study of 182 patients and 195 control subjects was commenced by the neurology divisions of seven clinical centers. The patients were divided into five diagnostic categories: transient ischemic attacks, thrombosis-in-evolution, thrombosis, cerebral embolism, and a thrombosis or embolism group. The last cerebrovascular episode had occurred in all patients within eight weeks before admission to the study. The conclusion reached is that long-term anticoagulant therapy does not appear to reduce the mortality in occlusive cerebrovascular disease and is associated with an added risk of death due to hemorrhagic complications.

STUDIES OF THE EFFECTS OF PHENMETRAZINE (PRELUDIN) IN CARDIOVASCULAR DISEASE

Fletcher, L., Jr.; Torosdag, S., and Bryant, J. M. *Am. J. M. Sc.* **241:** 491 (Apr.) 1961.

In normotensive persons, 10 to 25 mg. of phenmetrazine intravenously exerted a pressor effect (within five to ten minutes) that was about one-fifth as potent, on a milligram basis, as that noted with dextroamphetamine. Two reactivity patterns were noted in hypertensive subjects. In one, 2 hypertensive subjects experienced a potent pressor effect with a rise in the systolic and diastolic blood pressures analogous to the changes seen in persons with normal blood pressure. A step-wise additive effect was noted when the drug was administered at thirty-minute intervals. The other pattern in hypertensive persons was no appreciable change in pulse rate, blood pressure, or electrocardiogram and no stepwise additive effect upon repeated intravenous dosage. These results may have been due to the presence either of "fixed" or "labile" types of hypertension. During long-term administration, phenmetrazine decreased the appetite with resultant weight loss without causing other undesirable cardiovascular effects. It is concluded that the benefits from phenmetrazine in obese patients with cardiovascular disease outweigh any conventional objections to its use. Obese cardiac and hypertensive patients show no adverse effects from its use in therapeutic dosage.

ASPETTO ISTOLOGICO DEL TESSUTO SINOVIALE NELL'ETÀ SENILE (THE HISTOLOGIC ASPECTS OF THE SYNOVIAL TISSUE IN OLD AGE).

Garelli, R. *Reumatismo* **11:** 334, 1959; through Excerpta med. (Gerontol. & Geriatrics) **4:** 60, 1961.

The finer structural modifications of the synovial tissue in old age were studied by comparing the histologic autopsy findings on the synovial tissue of the articular cartilage of the knee obtained in a group of persons deceased between 20 and 40 years of age and those obtained in a group deceased between 60 and 80 years. It was found that in old age the synovial layer is thinner, that there is a larger number of folds and of synovial villi, that the synovial cellular elements are less rich in cytoplasm, that the fibrillary stroma shows increased density, that the ground substance is less abundant, and that the reticular fibers exhibit marked degenerative processes. Moreover, the connective tissue beneath the synovial lining in old age shows an increase in the stromal component, and a decrease of the ground substance and of the cells; further, it shows a moderate increase of the number of elastic fibers which, however, show regressive processes. In the author's opinion, the finer alterations of the structure shown by the synovial and subsynovial tissue in old age, suggest that with advancing age these tissues are changed not only in their physical properties, but also in their metabolic and reactive functional activities.

PRECURSORS OF CORPUS CANCER. III. THE APPEARANCE OF CANCER OF THE ENDOMETRIUM IN ESTROGENICALLY CONDITIONED PATIENTS.

Gusberg, S. B., and Hall, R. E. *Obst. & Gynec.* **17:** 397 (Apr.) 1961.

Data and microphotographs of histologic sections from estrogenically conditioned tumors in 23 patients are presented. These patients with adenocarcinoma of the endometrium had received estrogens continuously, 12 for one to five years, 7 for six to ten years, and 5 for more than ten years. The type of estrogen included stilbestrol, estradiol benzoate, ethinyl estradiol, estrone, and in 8 cases undefined estrogen therapy. The presenting symptom of endometrial carcinoma was postmenopausal bleeding in 16 patients, menorrhagia or metrorrhagia in 3, and unknown in 6. Treatment consisted of hysterectomy alone or combined with radiation therapy. One patient died within a year and 1, seventeen years after treatment. One had a local recurrence that was successfully treated surgically. The tumors histologically resembled adenomatous hyperplasia of the endometrium but had malignant qualities in their structural pattern. They shared the properties of budding, crowding, eosinophilic staining, pseudostratification, and microfollicular reduplication. The cancer pattern was papillary, well differentiated, and usually confined to the endometrium. There was invasion of the myometrium in 6 patients and widespread metastases in 2 patients. The resemblance of the lesions to adenomatous hyperplasia that can be produced by estrogens, and to lesions seen in the endometrium of patients with estrogen-producing ovarian tumors, led to the conclusion that estrogen played a role in the development of these tumors.

ABSORPTION OF I^{131}-LABELED ALBUMIN IN CONGESTIVE HEART FAILURE.

Hakkila, J., and Mäkelä, T. E. *Acta med. scandinav.* **169**(3): 237, 1961.

The intestinal absorption of I^{131}-labeled serum albumin was studied in 10 control subjects and 10 patients with congestive heart failure. The mean radioactivity values in the blood in patients with heart failure were in the low-normal range. The mean excretion of radioactivity in the feces during a three-day period was 1.2 per cent of the ingested dose in the control subjects and 2.2 per cent in the patients with congestive heart failure. In view of the finding of a nearly normal absorption of I^{131}-labeled oleic acid, the present results seem to support the opinion that the marked disturbance in absorption of I^{131}-triolein seen in patients with congestive heart failure should be ascribed not to altered pancreatic function, but rather to disturbed bile secretion. (Authors' summary.)

LA RÉCEPTIVITÉ AUX ESTROGÈNES APRÈS LA MÉNOPAUSE. (THE RECEPTIVITY TO ESTROGENS AFTER THE CLIMACTERIC.)

Herschberg, A. D. *Rev. franç. gérontol.* **5:** 281, 1959; through Excerpta med. (Gerontol. & Geriatrics) **4:** 89, 1961.

After recalling the present definition of hormonal receptors and showing that the receptivity to estrogens depends mostly on the richness of the target organs in trophic nerves, the author studied the sensitivity to estrogens in the aging female. Different receptors have an individual response threshold for the hormone; this threshold is lowered by an inflammatory or dystrophic state of the organ. Thus, sensitivity is higher in an endometritis or in a chronic cystic mastitis. Sclerous lesions increase the response threshold and lower the sensitivity. These facts explain that the variation of estrogen receptivity during the menopause depends particularly on the pathologic past and present of the target organs. Physiologically, there is an elevation of estrogen sensitivity during the premenopausal period and a steep decrease after definitive amenorrhea. But this regression of sensitivity varies with different receptors; it is much slower in the endometrium than in the vagina or the mammae. The author often observed atrophic vaginitis accompanied by an almost normal endometrium. In the postmenopausal period, there are some cases of pathologic hypersensitivity to estrogens in one or several target organs, which may last for five to ten years after the amenorrhea. The skin test with hydrosoluble estrone sulfate, previously proposed by the author, is a quick and easy means for detecting these cases.

FACTORS INFLUENCING RESPONSE TO HYPOPHYSECTOMY FOR ADVANCED CANCER OF BREAST.

McCalister, A.; Welbourn, R. B.; Edelstyn, G. J. A.; Lyons, A. R.; Taylor, A. R.; Gleadhill, C. A.; Gordon, D. S., and Cole, J. O. Y. *Brit. M. J.* **1:** 613 (March 4) 1961.

In an analysis of advanced breast cancer in 75 women, three factors were found to influence the result significantly: 1) the site of the lesions, 2) the relation to the menopause, and 3) the time at which the operation was performed. Factor 1: Patients with osseous metastases fared better than those with local disease or visceral metastases only. This factor was most effective in premenopausal patients. The outcome was not influenced by the presence of the primary lesion at the time of hypophysectomy. The presence of visceral metastases, even in patients with osseous lesions, adversely affected the prognosis. Factor 2: Remission occurred in a higher proportion of patients who were still menstruating than among those who had had a natural menopause or had undergone oophorectomy. This factor appeared in the osseous group and also in patients who had early or late operations. In the case of soft-tissue lesions, remissions were seen only in postmenopausal patients, but this result may have been due to chance. Factor 3: A higher proportion of objective remissions occurred among patients who underwent hypophysectomy within six months after the time that the disease became uncontrolled than among patients whose operation was performed after that time. The total duration of the disease from the time of appearance of the primary breast cancer to hypophysectomy, the age, and the histologic structure of the tumor did not influence the result. The data appeared to indicate that patients with osseous metastases who underwent hypophysectomy as the first endocrine maneuver fared better than patients who received endocrine therapy first. The survival period, however, seemed to be longer in those who received simple endocrine therapy first.

INVESTIGATIONS ON THE GLYCOPROTEIN COMPOUNDS IN THE BLOOD AND URINE AS RELATED TO AGE AND THE THYROID SYNDROMES.

Milcu, St. M.; Spandonide, T.; Mihaiescu, C., and Mihaiescu, E. *Gerontol. Clin.* **3**(1): 25, 1961.

The concentration in the blood of total protein-bound hexoses, total hexosamines, fucose, serum mucoid proteins expressed as tyrosine and hexose, sialic acid (by means of Dische's

test), total proteins, serum albumins and serum globulins as well as the urinary elimination of serum mucoprotein was determined in five groups of subjects: 1) normal subjects, 20 to 40 years of age; 2) normal subjects, 50 to 60 years of age; 3) normal subjects, 70 to 80 years of age; 4) patients 50 to 60 years of age with hyperthyroidism; and 5) patients 50 to 60 years of age with hypothyroidism. Statistically significant increases were found in relation to age in hexosamines, fucose, sialic acid, and urinary mucoprotein. Compared with normal subjects in the same age groups, the hypo- and hyperthyroid subjects showed significant increases in the protein fraction of the serum mucoproteins. Although no explanation for these increases related to age are at hand, the variations cannot be ascribed to the alterations of total proteins or to the albumin fractions, nor to that of the globulin fraction of total proteins. The excretion of urinary mucoproteins is not linked with the mucoprotein concentration of the blood. The results indicate that the increases in the protein fractions of the serum mucoid proteins in both hypo- and hyperfunction of the thyroid might originate in a common endocrine factor. The increases in concentration of glycoprotein fractions occurring with age may lend support to the theory that penetration of the glycoproteins into the arterial wall might constitute an essential preceding phenomenon in the process of arteriosclerosis.

THIOTEPA IN CARCINOMA OF BREAST TREATED BY BILATERAL ADRENALECTOMY AND OOPHORECTOMY.

Miller, A. B. *Brit. M. J.* **1:** 619 (March 4) 1961.

Twelve women with metastatic carcinoma of the breast, who had been subjected to bilateral adrenalectomy and oophorectomy, were treated with methyltestosterone and thioTEPA. All except 3 had had a radical mastectomy. Only 5 of the group had been improved following the two former procedures; 6 of 9 patients who received methyltestosterone could not tolerate it. ThioTEPA produced temporary improvement with palliation in 2 patients but none in the other 10 patients. One of the patients who improved had received methyltestosterone but the other had not. The dosage of thioTEPA appeared to be adequate (15 mg. three times weekly for two weeks, and then 15 mg. weekly by intramuscular injection) since significant leukopenia occurred in more than half of the patients, but the dosage was small in comparison with that used in other studies. The failure of treatment may have been due in part to the fact that it was started at an advanced stage of the disease. However, some of those who failed to respond were patients who initially had responded to bilateral adrenalectomy and oophorectomy. The administration of thioTEPA had a good effect on the morale of the patients.

A HEMODYNAMIC STUDY OF HYPERTENSION INCLUDING OBSERVATIONS ON CORONARY BLOOD FLOW.

Rowe, G. G.; Castillo, C. A.; Maxwell, G. M., and Crumpton, C. W. *Ann. Int. Med.* **54:** 405 (March) 1961.

Hemodynamic data are presented for a series of 21 hypertensive subjects and these are compared with data for 30 normotensive subjects. In the 14 subjects with Smithwick grades 1 and 2 hypertension (Group I) the cardiac index was normal, whereas in the 7 subjects with grades 3 and 4 hypertension (Group II) the cardiac index was reduced. Total peripheral vascular resistance was elevated in both groups of hypertensive subjects and was significantly higher in Group II than in Group I. Total pulmonary resistance was elevated only in the Group II subjects. The left ventricular work index was elevated in Group I hypertensive subjects, but normal in Group II. The right ventricular work index was normal in Group I but reduced in Group II. Coronary blood flow was normal in both groups, as was myocardial oxygen consumption per 100 Gm.; however, coronary vascular resistance was significantly elevated in both groups of hypertensive subjects. It is concluded that cardiac efficiency must be reduced in Group II, since myocardial oxygen consumption per

unit of weight was normal, myocardial weight was high, and cardiac work was normal. (Authors' conclusions.)

SPONTANEOUS ATLANTO-AXIAL DISLOCATION IN ANKYLOSING SPONDYLITIS AND RHEUMATOID ARTHRITIS.

Sharp, J., and Purser, D. W. *Ann. Rheum. Dis.* **20:** 47 (March) 1961.

From a study of radiographs of the cervical spine of samples of the general population, it was concluded that after age 45 a separation of more than 3 mm. of the odontoid process from the anterior arch of the atlas on a conventional lateral film is usually abnormal and highly likely to be associated with rheumatoid arthritis, though in younger subjects a gap of 4 mm. may be normal. The clinical studies suggest that occasionally a gap of even 3 mm. may be abnormal. The prevalence of atlantoaxial displacement, so defined, in members of the general population with evidence of rheumatoid arthritis was 32 per thousand; in those with clinical evidence of the disease, 64 per thousand; and in those with rheumatoid arthritis admitted to hospital, 189 per thousand. The lesion was observed much less frequently in ankylosing spondylitis, but a prevalence rate could not be established. In a study of 22 patients with ankylosing spondylitis and 26 with rheumatoid arthritis in whom spontaneous displacements of the atlas on the axis had developed, there was invariably clinical evidence of the displacement in spondylitis but not in a substantial proportion of patients with rheumatoid arthritis. The diagnosis in such cases was made from radiographs taken with the neck extended and flexed. The clinical features of the displacement were: 1) pain in the upper part of the neck radiating to the occipital and sometimes to the temporal and frontal regions, greatly aggravated by jarring movements; 2) difficulty in raising the head after looking down, often accompanied by difficulty in shaving under the chin and a sensation of "falling forward" of the head; and 3) flattening of the occipito-cervical curve, often accompanied by some degree of torticollis. In a few instances (6 cases of rheumatoid arthritis and 7 cases of spondylitis), the presenting manifestations were signs of damage to the spinal cord. The severity of the neurologic changes was correlated roughly with the degree of narrowing of the spinal canal, but some patients escaped damage to the cord in spite of a gross degree of displacement. Spontaneous stabilization of the displacement may occur without treatment, but it is not known how often this occurs, and in both conditions displacements were observed to progress in some untreated patients. The majority therefore were treated by supporting collars, usually with relief of pain and sometimes with reduction both of the degree of displacement and of the abnormal mobility. Four of the patients with rheumatoid arthritis were treated by occipito-cervical fusion, the indication for operation being the presence of neurologic signs. This also was the primary indication for operation in 11 patients with spondylitis; the primary indications in the others were pain in 5, severe deformity in 1, and progression of the displacement despite a collar in 1. With the exception of 1 rheumatoid patient in whom fusion was unsuccessful and who later died from septicemia, the results of operation were excellent; local symptoms were relieved and major improvement occurred in patients with cord damage. (From authors' summary.)

ELECTROMYOGRAPHIC CHANGES IN RHEUMATOID ARTHRITIS.

Steinberg, V. L., and Parry, C. B. W. *Brit. M. J.* **1:** 630 (March 4) 1961.

Electromyograms and intensity duration curves were obtained on 93 patients with rheumatoid arthritis. The muscles selected were the small muscles of the hand, the deltoid, the biceps, and the quadriceps. Electromyographic evidence of polymyositis was found in one or more muscles in 79 patients (85 per cent). Results of sheep cell agglutination tests were more frequently positive in patients with polymyositis. Intensity duration curves showed partial denervation in 37 of the muscles showing polymyositis and in 2 muscles with a normal electromyograph. The electromyographic changes were not due to wasting; several muscles with wasting showed a normal electromyogram and several without wasting showed the changes of polymyositis. Positive findings, however, did bear a relation to disease ac-

tivity, although the changes on rare occasion were found in inactive cases. The changes did not represent a steroid myopathy since only a few of the group had received steroids. This study supports the belief that neuromuscular abnormality is common in rheumatoid arthritis and is another systemic manifestation of the disease.

COLCHICINE. CLINICAL PHARMACOLOGY IN ACUTE GOUTY ARTHRITIS.
Wallace, S. L. *Am. J. Med.* **30:** 439 (March) 1961.

Modification of the colchicine molecule on the side-chains of the first (benzene), second or third rings does not abolish anti-gout activity, as long as the spatial configuration in the third ring conforms to that of the parent drug. Colchiceine, a derivative of isocolchicine, has side-chains on the third ring with different spatial arrangements from those of colchicine; it is ineffective in the treatment of acute gout. Colchicine given orally is absorbed in the gastro-intestinal tract, passes through the liver, and re-enters the intestine by way of the biliary tract. Some is reabsorbed from the intestine. Urinary excretion of unchanged colchicine is reported by some but denied by others. In any event, colchicine disappears rapidly from the blood, and is not measurable in the brain, heart or muscle. The mechanism of action of colchicine in acute gouty arthritis is as poorly understood as the pathogenesis of the attack itself. Colchicine, when given in therapeutic doses, does not seem to have any significant effect on uric acid metabolism or on adrenocortical function. As far as can be determined, its anti-gout activity is not related directly in any way to its anti-mitotic effects, nor is it dependent upon the production of diarrhea. The drug has been shown to have a distinct action on the central nervous system. In sufficient concentrations it affects a variety of enzyme systems. It is possible that its potent anti-gout action is related to one of these areas. The use of colchicine, both orally and intravenously, has been reviewed. Desacetylmethylcolchicine, an analogue of colchicine, has been shown to be both effective in acute gouty arthritis and more toxic than the parent drug. Trimethylcolchicinic acid, another analogue, is both effective and nontoxic when used in therapeutic dosages. Finally, colchicine has been shown to have toxicity in addition to its well known gastro-intestinal side-effects. In sensitive subjects, leukopenia, bone marrow depression, loss of hair, nerve damage, and death have been reported to follow doses little larger than those used in the treatment of gout in some patients. Such reactions, however, have rarely been observed. (Author's conclusions.)

BACTERIAL ENDOCARDITIS IN OLD AGE.
Wedgwood, J. *Gerontol. Clin.* **3:** (Suppl.): 11–23, 1961.

Thirteen cases of subacute and 2 cases of acute bacterial endocarditis in persons over 60 years of age are described. The disease runs a more quiet and insidious course in old age than in younger patients. It may present in bizarre ways, as with mental confusion, gastro-intestinal symptoms and weight loss, or with symptoms of renal or hepatic disease. In old age there are likely to be more alternative explanations for these symptoms than in younger persons so that the diagnosis may be missed. Because the disease is not suspected, its signs may not be vigorously sought. It is essential to recognize the significance of signs of valvular heart disease which occur in nearly all cases. Fever may be intermittent or low-grade so that four-hourly temperature readings are necessary. The sedimentation rate is always elevated. Blood culture findings can be positive in the presence of little or no fever. Therapy should not be delayed waiting for the results of cultures when the diagnosis is reasonably certain. The importance of prophylaxis by penicillin in operations for dental extraction and minor operations of the urinary tract and lower bowel, especially in elderly patients with valvular heart disease, is emphasized. The acute form of bacterial endocarditis is less common. Diagnosis in such cases is urgent and treatment consists of large doses of penicillin.

CORTICOSTEROID BRUISING.

West, H. F. *Ann. Rheum. Dis.* **20:** 86 (March) 1961.

Although patients receiving long-term exogenous corticosteroid therapy are subject to pathologic bruising, this does not occur in patients treated with corticotropin. Fifty-eight patients receiving long-term corticosteroid therapy for rheumatoid arthritis and ankylosing spondylitis were examined repeatedly during a year for evidence of bruising. It occurred in 60 per cent of 40 receiving exogenous corticosteroids for at least two years, but in none of 18 receiving corticotropin for a similar period. The mean dose level was 10 mg. of prednisolone or an equivalent dose of triamcinolone or dexamethasone. The mean dose level in the corticotropin group (as 17-hydroxycorticosteroids excreted daily) was 22 mg. More women (83 per cent) were affected than men (20 per cent). Between affected and unaffected groups of females there was little difference, if any, with respect to sedimentation rate, hemoglobin level, strength of grip, blood pressure, weight, or functional capacity. Patients with the most severe and damaging leg bruising did have higher total leukocyte counts and had received more corticosteroid than the mean for the group. There was little difference in the mean adrenal contribution to 17-hydroxycorticosteroid excretion between affected and unaffected patients. This defect may be due either to a direct action of the exogenous corticosteroid on connective tissue, or to the loss of an adrenal hormone or the adrenocorticotropic hormone caused by the administration of the exogenous steroid. If an elevated level of circulating hydrocortisone can cause bruising, the absence of bruising during corticotropin therapy may be due to the concurrent secretion of a compensating adrenal hormone or of corticotropin.

RENAL FUNCTION IN THE AGED.

Woodford-Williams, E. *Brit. J. Clin. Pract.* **14:** 351, 1960; through Excerpta med. (Gerontol. & Geriatrics) **4:** 66, 1961.

Any estimate of renal function, or of the function of any other organ in the aged, must take into consideration the effect of previous injury or disease. Normal data can be obtained only on persons with no history of renal or cardiovascular disease who have a diastolic blood pressure less than 90 mm. Hg, and no evidence of prostatism nor any abnormality in the urine (which should have a specific gravity no less than 1.020 after fourteen hours without fluid). The glomerular filtration rate declines with age. Hypertension is associated with a greater decline. Renal blood flow, measured by Diodrast clearance, is substantially less in the aged. The filtration fraction is increased and the increase is greater in hypertensive patients. After administration of pyrogen, the blood pressure falls but renal blood flow increases in all age groups. Renal resistance calculated from Lamport's formula is higher in the aged than in the young, both before and after pyrogen administration, but the percentage decrease in resistance after pyrogen is greater in the aged, suggesting an increased vasoconstrictor element operating in the aged. The ratio between glomerular filtration and maximum tubular excretory capacity for Diodone (tubular function) remains constant, indicating that glomeruli and tubules are lost in equal numbers. Tubular function may be measured by the water concentration test of Volhard in the modification of Fishberg. The specific gravity declines with age but should be at least 1.021. The maximal tubular excreting power diminishes with age, as does the reabsorptive power of the tubules for glucose. From ages 30 to 90 years the decline is about 40 per cent. In uninfected prostatic disease, tubular function was normal but the glomerular filtration rate and renal plasma flow were reduced to two-thirds of the normal for the aged. In the infected group, however, all three functions were diminished. This reduction of tubular function in the presence of infection is due to pyelonephritis. The high incidence of pyelonephritis is frequently overlooked. In a series of 670 consecutive post mortems of aged people, 9 per cent were found to have died from genito-urinary disease, and 64 per cent of these showed evidence of pyelonephritis.

NEWS AND NOTICES

CALL FOR PAPERS

The 19th Annual Meeting of the American Geriatrics Society will be held at the Palmer House, Chicago, Illinois, on Monday, Tuesday and Wednesday, *June 18, 19 and 20, 1962.*

Abstracts of papers for this meeting should be submitted to the Chairman of the Program Committee for consideration. Abstracts should be submitted in duplicate, double spaced, and include the title, author(s), etc. The text of the abstracts should be a complete synopsis so that the reviewer may adequately evaluate the complete work. The author should indicate at the end of the abstract whether he would present lantern slides or moving pictures (size; sound or silent). Abstracts are limited to 250 words.

Each speaker may use 20 minutes for his paper, followed by a 5-minute discussion period. Moderators will be asked to enforce the 25-minute period. Speakers are urged to check the length of their presentation.

Before January 1, 1962 send abstracts to: Program Chairman, American Geriatrics Society, 2907 Post Road, Warwick, Rhode Island.

BOOKS RECEIVED

Receipt of the following books for review is hereby acknowledged. We are glad to publish complete listings of all new books received but such listing must be regarded as a sufficient return for the courtesy of the sender. Books of particular interest will be reviewed in full as time and space permit. Additional information in regard to all listed books will be gladly furnished upon request.

AGING: SOME SOCIAL AND BIOLOGICAL ASPECTS. Symposia presented at the Chicago Meeting of the American Association for the Advancement of Science, December 29–30, 1959. Edited by *Nathan W. Shock*. Cloth. $8.50—Prepaid to AAAS members, $7.50. Pp. 436. American Association for the Advancement of Science, 1515 Massachusetts Avenue, N.W., Washington 5, D. C.

ESSENTIAL HYPERTENSION—An International Symposium, Berne, June 7–10, 1960. Chairman, *H. Schwiegk*, Munich. Edited by *K. D. Bock*, Basle, and *P. T. Cottier*, Berne. Cloth. $8.45. Pp. 392, with 81 figures. Springer-Verlag, Berlin-Göttingen-Heidelberg, 1960.

THE DAY HOSPITAL MOVEMENT IN GREAT BRITAIN. An Analysis and Description of Sixty-five Day Hospitals and Day Centres with Special Reference to Psychiatric and Geriatric Day Hospitals Visited in 1958–9. By *James Farndale, B. Com., F.H.A., M.R.S.H.* Cloth. $15.00. Pp. 430. Pergamon Press Ltd., Headington Hill Hall, Oxford, England, 1961.

ARTERIOSKLEROSE: Ätiologie, Pathologie, Klinik und Therapie. Edited by *Prof. Dr. Gotthard Schettler*, Director der Medizinschen Klinik Stuttgart-Bad Cannstatt. Cloth. $24.50. Pp. 728, with 149 illustrations. Georg Thieme Verlag, Stuttgart, Herdweg 63, Germany. In the U.S.A. and Canada, Intercontinental Medical Book Corporation, New York 16, N. Y., 1961.

ALTERSFORSCHUNG UND ALTERSBEHANDLUNG—Einige Aspekte der Physiologie, Pathologie und Therapie des Alterns. By *Dr. med. Paul Luth*. Paper. Pp. 163. E. Merck AG, Darmstadt, Germany, 1961.

MYXEDEMA. By *Jerry K. Aikawa, M.D.*, Associate Professor of Medicine, University of Colorado School of Medicine, Denver, Colorado. Cloth. Pp. 106. Charles C Thomas, Publisher, Springfield, Illinois, 1961.

Books for review should be sent to Edward Henderson, M.D., Editor-in-Chief, 236 Midland Avenue, Montclair, New Jersey.